Sponsor Briefing Document

FDA Pulmonary - Allergy Drugs Advisory Committee

Orkambi (Lumacaftor/Ivacaftor) for the Treatment of Cystic Fibrosis in Patients Age 12 Years and Older Who Are Homozygous for the *F508del* Mutation in the *CFTR* Gene

NDA 206038

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1 EXECUTIVE SUMMARY

1.1 Proposed Indication for ORKAMBI™ (Lumacaftor/Ivacaftor)

Orkambi (lumacaftor in combination with ivacaftor [LUM/IVA]) is the first medicine designed to treat the underlying cause of cystic fibrosis (CF) in people who are homozygous for the *F508del* mutation, the most prevalent *CFTR* genotype in the CF patient population.

In November 2014, Vertex submitted an NDA for the approval of Orkambi for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Orkambi is supplied as tablets containing both LUM 200 mg and IVA 125 mg. The recommended dosage is 2 tablets taken orally every 12 hours (q12h).

1.2 Disease Background and Medical Need

CF is a progressive, systemic, life-shortening, genetic disease that affects about 30,000 people in the United States.

CF is caused by reduced quantity and/or function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in multiple organs, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR chloride transport results in multisystem pathology[1], beginning at birth. In 2013, the median age of death for people with CF in the United States (US) was 27.5 years.[2]

Lung disease is the primary cause of morbidity and mortality in people with CF.[2,3] In the lungs, the pathology consists of a cycle of mucus obstruction, infection, and inflammation that leads to irreversible structural changes in the lungs, progressive decline in lung function, and eventually respiratory failure.[4] The average rate of lung function decline across the CF population is estimated at 1% to 3% per year.[5] Pulmonary exacerbations, discrete events that occur throughout the life of a CF patient, are characterized by worsening respiratory symptoms that often require treatment with antibiotics and/or hospitalization. Exacerbations are associated with a more rapid rate of decline in lung function[6-8] and have a negative impact on 5-year survival.[9,10]

Non-pulmonary aspects of CF also significantly affect the course of disease and patient outcomes. For example, poor nutritional status is common due to a number of factors, including pancreatic insufficiency, malabsorption, and chronic lung inflammation.[3,11] A higher body mass index (BMI) is associated with better lung function,[2] and BMI is an independent predictor of mortality.[12-14]

See Section 2 for more information about CF.

No medicine targeting the underlying cause of disease is available for the majority of people with CF.

Three important goals of CF treatment are to maintain lung function, reduce the frequency of pulmonary exacerbations, and improve nutritional status. With the exception of IVA, current treatments for CF target only the downstream consequences of the disease. These treatments include inhaled mucolytics, bronchodilators, antibiotics, anti-inflammatory medicines, and pancreatic enzymes.[15,16]

IVA is a precision medicine that is indicated for a specific subset of CF patients: those with a mutation that result in CFTR protein with a primary defect of decreased channel gating (decreased open probability). Treatment with IVA results in multiple downstream benefits, including improvements in lung function, decreased risk of pulmonary exacerbations, and improvements in measures of nutritional status (see Kalydeco USPI). Furthermore, results from analysis of long-term treatment of patients with the *G551D* mutation (the most prevalent mutation for which IVA is approved) show that treatment with IVA can slow the rate of decline in forced expiratory volume in 1 second (FEV_1) and thus, modify the course of the disease.[17]

The population for which IVA is currently approved includes about 1950 patients in the US. For the remainder of the CF patient population, there is a need for more effective treatments.

See Section 2.6 for more information about current treatments.

***F508del* is the most prevalent CF-causing mutation. In the US, about 50% of people with CF are homozygous for *F508del*. This population typically has a severe form of CF.**

In the US, about 14,000 people with CF are homozygous for the *F508del-CFTR* mutation, including about 8,500 people age 12 years and older. The *F508del* mutation causes a severe defect in the processing and trafficking of CFTR, resulting in little-to-no CFTR protein at the cell surface.[18-24] Because of the near-complete loss of CFTR chloride transport, the *F508del/F508del* mutation is typically associated with a severe form of CF, characterized by high sweat chloride concentrations, a rapid rate of lung function decline, frequent colonization of the sinuses and lungs with *Pseudomonas aeruginosa*, a high incidence of pancreatic insufficiency, and reduced life expectancy.[25-30]

1.3 Mechanism of Action and In Vitro Results

LUM and IVA have complementary mechanisms of action. In combination, LUM and IVA target the molecular defect and enhance the function of F508del-CFTR.

IVA is a CFTR potentiator that increases the channel-open probability ("gating"; proportion of time the channel is open) of CFTR protein at the cell surface. In contrast to the mutations for which IVA is currently approved, *F508del* causes a severe defect in CFTR protein processing and trafficking, resulting in little-to-no CFTR at the cell surface.[18-24] Because of this, it was clear that an additional medicine would be needed to address the underlying defect in people homozygous for *F508del*.

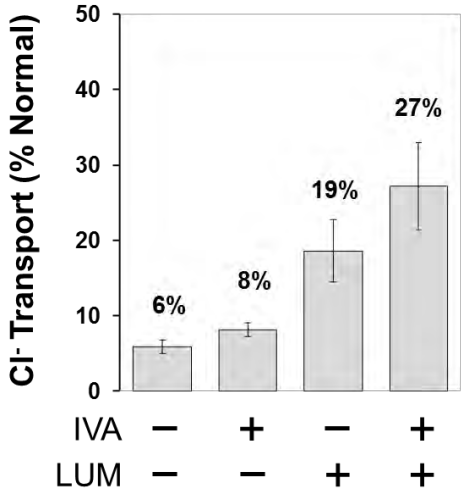
LUM is a CFTR corrector that improves the processing and trafficking of the F508del-CFTR protein, resulting in an increase in the quantity of F508del-CFTR protein at the cell surface. IVA increases the channel open probability of the F508del-CFTR protein delivered to the cell surface by LUM, thereby enhancing total chloride transport. In the absence of LUM, there is very little F508del-CFTR protein at the cell surface for IVA to potentiate. The combined effect of LUM and IVA is increased quantity and function of F508del-CFTR at the cell surface.

See Section 3 for more information about CFTR correctors and potentiators. Section 3.4 provides further details about the mechanism of action studies.

In vitro studies of *F508del/F508del*-HBE cells (human bronchial epithelial cells derived from people homozygous for *F508del*) demonstrated that LUM/IVA treatment increases F508del-CFTR chloride transport and is superior to the effect of either drug alone.

In *F508del/F508del*-HBE cells, IVA alone had minimal effect on chloride transport, consistent with there being little-to-no F508del-CFTR protein at the cell surface (Figure 1). LUM increased chloride transport to 19% of normal, consistent with LUM directly addressing the defect caused by *F508del* to increase the amount of F508del-CFTR protein at the cell surface. LUM/IVA in combination increased chloride transport to 27% of normal, a greater increase then either drug alone, and consistent with the complimentary mechanisms of action of LUM and IVA.

Figure 1 CFTR Chloride Transport in F508del/F508del-HBE Cells Treated With IVA, LUM, or LUM/IVA



Forskolin-stimulated chloride transport in *F508del/F508del*-HBE cells derived from a 4 donor bronchi treated for 24 hours with vehicle, 0.1 µM IVA, 3 µM LUM, or 3 µM LUM and 0.1 µM IVA. Data are presented as the mean (± SEM) from 4 donor bronchi.

1.4 Phase 2 Program

The Phase 2 program in people homozygous for *F508del* was designed to (1) determine if the combination of LUM and IVA is more effective than either drug alone, (2) evaluate the safety profile of the selected therapy to further assess in Phase 3 studies, and (3) determine the dose for Phase 3 studies.

Phase 2 studies evaluated IVA monotherapy, LUM monotherapy, and LUM/IVA combination therapy in patients homozygous for *F508del*. These studies included assessments of sweat chloride concentrations and lung function (percent predicted FEV_1 [$ppFEV_1$]). Sweat chloride concentrations provide a direct measure of CFTR function in the sweat gland: a reduction in sweat chloride indicates enhanced CFTR function in vivo.

IVA monotherapy was not effective in patients homozygous for *F508del*.

Before the Phase 2 study evaluating LUM monotherapy and LUM/IVA combination therapy (Study 102) was initiated, a placebo-controlled, Phase 2 study was conducted to evaluate IVA monotherapy in patients homozygous for *F508del* (Study 770-104). IVA monotherapy (150 mg q12h) resulted in minimal change in sweat chloride, and the study did not meet the primary efficacy endpoint (absolute change in $ppFEV_1$ from baseline through Week 16) or any other efficacy endpoints (Table 9 on page 44).

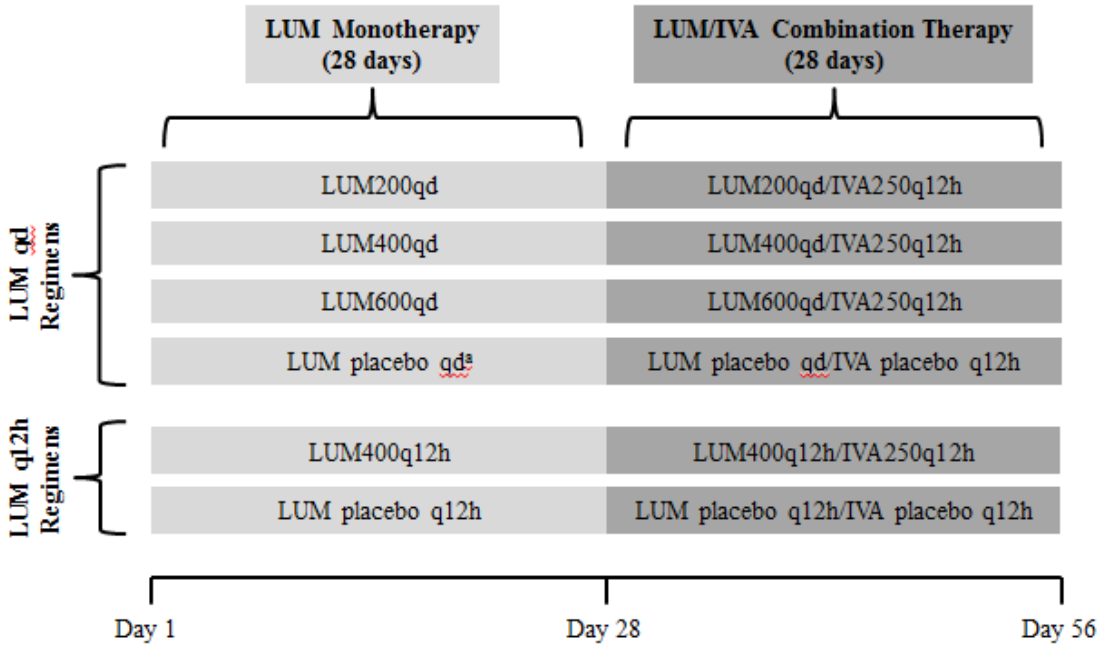
The results of Study 770-104 (including pharmacodynamic [PD] and clinical effects) were consistent with in vitro findings and the mechanistic understanding of the underlying defect in F508del-CFTR, which suggested that CFTR potentiation alone might not lead to clinical benefit because there is not enough F508del-CFTR protein on the cell surface to potentiate. Based on the consistent cumulative evidence, it was concluded that IVA alone is not effective in patients homozygous for *F508del* (see Kalydeco USPI).

See Section 5.1.1 for more information about Study 770-104.

LUM monotherapy decreased sweat chloride but did not increase $ppFEV_1$ in patients homozygous for *F508del*.

Study 102 was a Phase 2, placebo-controlled, parallel-group, multi-cohort study that evaluated LUM monotherapy and LUM/IVA combination therapy in CF patients homozygous for *F508del*. Each patient received LUM monotherapy for up to 28 days, immediately followed by LUM/IVA combination therapy for up to 28 days. The same doses of LUM (200 mg to 600 mg daily [qd] or 400 mg q12h) were evaluated during monotherapy and combination therapy. A dose of 150 mg q12h or 250 mg q12h of IVA was evaluated during the combination therapy. Figure 2 shows the longest duration of LUM monotherapy and LUM/IVA combination therapy evaluated in Study 102.

Figure 2 Schematic of Longest Duration of Treatments Evaluated in Study 102



[a] CF patients homozygous and heterozygous for F508del were included in this group.

Treatment with LUM monotherapy decreased sweat chloride concentrations, with the largest changes observed for the 3 highest doses (Table 1). This finding is consistent with the mechanism of action of LUM and the in vitro data showing that LUM increases the quantity of functional F508del-CFTR at the cell surface (Section 1.3). However, LUM monotherapy was unexpectedly associated with a dose-dependent decline in absolute change in $ppFEV_1$ (Table 1).

Table 1 Sweat Chloride and $ppFEV_1$ Assessments at Day 28 (End of LUM Monotherapy Dosing), Study 102

Endpoint	LUM200qd N = 21	LUM400qd N = 20	LUM600qd N = 20	LUM400q12h N = 11
Sweat chloride: Change from baseline at Day 28				
Treatment difference versus placebo (95% CI)	-4.9 (-9.5, -0.3) *P* = 0.038	-8.3 (-13.0, -3.6) *P*<0.001	-6.1 (-10.8, -1.4) *P* = 0.012	-8.2 (-14.1, -2.3) *P* = 0.007
Absolute change in $ppFEV_1$: Change from baseline at Day 28				
Treatment difference versus placebo (95% CI)	0.2 (-3.7, 4.2) *P* = 0.904	-1.4 (-5.4, 2.6) *P* = 0.497	-2.7 (-6.7, 1.4) *P* = 0.196	-4.6 (-9.6, 0.4) *P* = 0.069

LUM/IVA combination therapy decreased sweat chloride concentrations and increased ppFEV$_1$ in patients homozygous for *F508del*; these results were superior to those achieved with either drug alone.

Improvements in both sweat chloride and absolute change in ppFEV$_1$ were observed with LUM/IVA combination therapy. From Day 28 to Day 56 of Study 102, patients continued to receive the same dose of LUM with the addition of IVA 250 mg q12h (combination therapy). Day 56 results, therefore, represent the net effect of LUM/IVA combination and LUM monotherapy. An IVA dosage of 250 mg q12h was used in the combination regimens because LUM is a strong cytochrome P450 3A (CYP3A) inducer and IVA is a sensitive CYP3A substrate (see Section 1.5).

As shown in Table 2, the two regimens with the highest total daily dose of LUM (LUM600qd/IVA and LUM400q12h/IVA) showed consistent improvements in sweat chloride and the greatest improvements from baseline in absolute change in ppFEV$_1$. The results at the end of LUM/IVA combination therapy (Day 56) were also compared to results at the end of LUM monotherapy (Day 28); as expected, given the decline in ppFEV$_1$ with LUM monotherapy, the largest improvements in absolute change in ppFEV$_1$ were observed with LUM600qd/IVA (6.2 percentage points; data not shown) and LUM400q12h/IVA (6.1 percentage points; data not shown).

Table 2 Sweat Chloride and ppFEV$_1$ Assessments at Day 56 (End of LUM/IVA Combination Dosing), Study 102

Endpoint	LUM200qd/IVA N = 21	LUM400qd/IVA N = 20	LUM600qd/IVA N = 20	LUM400q12h/IVA N = 11
Sweat chloride: Change from baseline at Day 56				
Treatment difference versus placebo (95% CI)	-5.0 (-10.5, 0.5) *P* = 0.073	-9.8 (-15.3, -4.3) *P*<0.001	-9.5 (-15.1, -3.9) *P* = 0.001	-11.0 (-18.3, -3.7) *P* = 0.004
Absolute change in ppFEV$_1$: Change from baseline at Day 56				
Treatment difference versus placebo (95% CI)	3.8 (-0.5, 8.1) *P* = 0.082	2.7 (-1.7, 7.0) *P* = 0.228	5.6 (1.2, 10.0) *P* = 0.014	4.2 (-1.3, 9.7) *P* = 0.137

LUM/IVA combination therapy was well tolerated

Overall, LUM monotherapy and LUM/IVA combination therapy was well tolerated in Study 102. The majority of adverse events (AEs) were mild or moderate in severity and were consistent with the expected manifestations of CF disease. The most common AEs during LUM monotherapy and LUM/IVA combination therapy observed in the active treatment groups and placebo groups were cough, infective pulmonary exacerbation of CF, headache, productive cough, upper respiratory tract infection, nausea, hemoptysis, respiration abnormal (verbatim term: respiratory chest tightness), and dyspnea. There were no consistent clinically important trends attributable to LUM/IVA combination in the clinical laboratory results.

The AEs of dyspnea and respiration abnormal appeared potentially associated with LUM, as they occurred more commonly in subjects who received higher doses of LUM monotherapy compared with LUM/IVA combination therapy or placebo. Spirometry was assessed following dosing with LUM/IVA to investigate this finding further: short-term declines in absolute change in $ppFEV_1$ were observed immediately postdose in healthy subjects 18 years of age and older (Study 009) and in pediatric CF patients 6 through 11 years of age (Study 011). These $ppFEV_1$ declines were only rarely associated with AEs, and $ppFEV_1$ levels returned to, or near, baseline within 7 days of continued dosing; the effect was ameliorated by treatment with long-acting bronchodilators and reversed by treatment with short-acting inhaled bronchodilators. Based on these data, this effect was expected to be limited in duration and clinically manageable.

Two LUM/IVA dose regimens were selected for Phase 3 studies

In Study 102, the LUM600qd/IVA and LUM400q12h/IVA regimens demonstrated the largest improvement in absolute change in $ppFEV_1$ and consistent improvements in sweat chloride. Therefore, both regimens were included in the Phase 3 studies. The LUM400q12h/IVA regimen was included because of the simplicity of the dosing regimen and the potentially advantageous pharmacokinetic (PK) profile (the LUM400q12h/IVA regimen allows for an approximately 2-fold increase in the expected trough concentration relative to the LUM600qd/IVA regimen, and reduced peak-to-trough ratio while incurring only a modest increase in the total daily dose and exposure of LUM). The LUM600qd/IVA regimen was supplied as a combination of fixed-dose combination (FDC) tablets and IVA tablets; the LUM400q12h/IVA regimen was supplied as FDC tablets (Figure 33 on page 87).

Nonclinical and Phase 2 studies established that LUM/IVA combination therapy was superior to either drug alone across in vitro, PD, and clinical endpoints. Therefore, monotherapy arms were not included in the Phase 3 studies.

1.5 Clinical Pharmacology

LUM and IVA are orally bioavailable CFTR modulators. When given in combination, LUM decreases the exposures of IVA through induction of CYP3A. The mean terminal phase half-life ($t_{1/2}$) of LUM and IVA when given in combination are approximately 26 hours and 9 hours, respectively. Steady-state plasma concentrations of LUM and IVA are reached after approximately 7 days of dosing. LUM is not metabolized extensively in humans, with the majority of LUM excreted unchanged in the feces. IVA is extensively metabolized in humans by CYP3A and eliminated in the feces as metabolites. There is negligible urinary excretion of LUM and IVA as unchanged parent.

Because LUM is a strong CYP3A inducer and IVA is a sensitive CYP3A substrate, the dose of IVA in the combination regimen is 250 mg q12h (instead of the approved IVA monotherapy dosage of 150 mg q12h). With the 250 mg q12h dosage, IVA exposures in the combination regimens were lower than those with IVA 150 mg q12h as monotherapy; however, the IVA exposures were expected to be adequate because IVA has a higher potency for F508del-CFTR than for G551D-CFTR.

Although LUM is a strong inducer of CYP3A, minimal clinically relevant drug interactions are expected with the major classes of common CF drugs, particularly with inhaled therapies. In some instances, a higher dose of the concomitant drug may be used to address the interaction. Several drug-drug interaction (DDI) studies were performed with LUM/IVA and guidance for the management of observed and anticipated DDIs is provided in the proposed labeling.

Additional information on the influence of a variety of demographic factors was obtained from population PK analysis. No dose adjustments of LUM/IVA are recommended on the basis of age, sex, or weight. A PK study in patients with moderate hepatic impairment (Child-Pugh B) indicated that dose adjustment of LUM/IVA combination therapy is needed for patients with moderate hepatic impairment (Child-Pugh B) to severe hepatic impairment (Child-Pugh C). In the thorough QTc study, LUM/IVA did not prolong the QTc interval.

As described in Section 1.4, Phase 3 studies used the LUM400q12h/IVA and LUM600qd/IVA regimens. The LUM400q12h/IVA regimen has a 33% higher total daily dose, and thus the difference in exposure was modest, with extensive overlaps in exposures for both LUM and IVA. The key differentiation between the two regimens is the approximately 2-fold higher LUM trough concentration and lower peak-to-trough ratio for the q12h regimen.

See Section 6 for more information about clinical pharmacology studies and exposures for the Phase 3 regimens.

1.6 Phase 3 Program

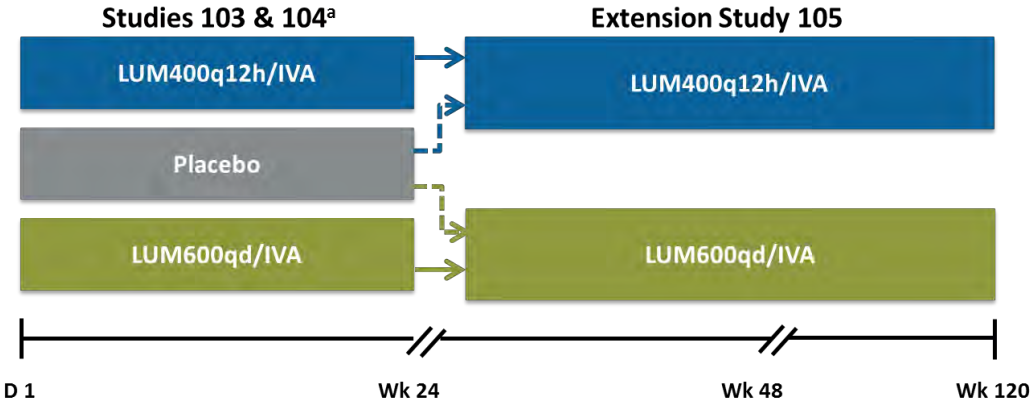
Two placebo-controlled, double-blind Phase 3 studies of LUM/IVA combination therapy were conducted in patients homozygous for *F508del* (Studies 103 and 104). Interim results from an ongoing extension study provide additional data for up to 24 additional weeks of treatment (Study 105).

Based on the results of the Phase 2 programs, and in consultation with US and European Union (EU) regulatory authorities, 2 pivotal, randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies (Studies 103 and 104) were designed to evaluate the efficacy and safety of LUM/IVA combination therapy in patients homozygous for *F508del* (Figure 3).

The studies were conducted at 187 sites in North America, Europe, and Australia, and enrolled patients aged 12 years and older with ppFEV$_1$ ≥40 to ≤90 whose CF disease was stable. In each study, patients were randomized 1:1:1 to receive LUM600qd/IVA, LUM400q12h/IVA, or placebo. Randomization was stratified by age, sex, and screening ppFEV$_1$. Patients took study drug in addition to their prescribed CF therapies.

Patients who completed Studies 103 or 104 and met eligibility criteria were offered the opportunity to enroll in Study 105, a long-term safety and efficacy rollover study. Patients treated with LUM/IVA in Study 103 or 104 continued to receive the same LUM/IVA dose regimen. Patients who received placebo in Study 103 or 104 were randomized in a 1:1 ratio to LUM600qd/IVA and LUM400q12h/IVA (Figure 3). Patients and study site staff were blinded to individual treatment assignment in Studies 103 and 104 and to the dose group in Study 105.

Figure 3 Phase 3 Program: Study Designs



[a] Studies 103 and 104 were identical except that Study 103 included assessment of ambulatory ECGs for a subset of US patients, and Study 104 included intensive PK sampling for a subset of US adolescent patients

The Phase 3 studies evaluated key clinical endpoints for CF, including FEV_1, measures of nutritional status, and pulmonary exacerbations.

In both studies, absolute change in $ppFEV_1$ was selected as the primary endpoint because FEV_1 is the most clinically accepted measure of disease progression in CF (Table 3). Key secondary endpoints assessed other important consequences of CFTR modulation on disease outcomes including pulmonary exacerbations and BMI, both of which require larger sample sizes and longer treatment duration to demonstrate improvement.

Table 3 Primary and Key Secondary Endpoints in Studies 103 and 104

	Endpoint
Primary[a]	Absolute change from baseline in $ppFEV_1$ at Week 24[b]
Key Secondary[a]	Relative change from baseline in $ppFEV_1$ at Week 24[b]
	Absolute change from baseline in BMI at Week 24
	Absolute change from baseline in CFQ-R respiratory domain at Week 24
	Patients with ≥5% increase in relative change from baseline in $ppFEV_1$[b]
	Number of pulmonary exacerbations through Week 24[c]

[a] The primary and key secondary endpoints are shown in the order of the testing hierarchy.
[b] Change in $ppFEV_1$ at Week 24 was assessed as the average of the treatment effects at Week 16 and at Week 24 to provide a more precise estimate of the treatment effect at the end of the treatment period, given the inherent variability in $ppFEV_1$.
[c] The definition of a pulmonary exacerbation was based on the modified Fuchs criteria[31] (Section 7.7.2).

Efficacy analyses for Studies 103 and 104 were prespecified to use the Full Analysis Set (FAS), defined as all randomized patients who received at least 1 dose of study drug. The primary analysis for the primary efficacy endpoint was based on a mixed-effects model for repeated measures (MMRM) that included adjustments for sex, age group at baseline, and $ppFEV_1$ severity at screening. All measurements up to Week 24 were included in analyses. For FEV_1-related endpoints, the primary result obtained from the model was the average treatment effect at Week 16 and at Week 24 to provide a more precise estimate of the treatment effect at the end of the treatment period, given the inherent variability in $ppFEV_1$.

Within Studies 103 and 104, a hierarchical testing procedure was used for each LUM/IVA group separately for the primary and key secondary endpoints at $\alpha = 0.0250$. At each step, the test for treatment effect was considered statistically significant if the *P* value was ≤0.0250 and all previous tests met this level of significance. Table 3 shows the primary and key secondary endpoints in the order of the testing hierarchy. If the testing hierarchy was broken, exploratory comparisons between active treatment and placebo were conducted for endpoints below the hierarchy and nominal *P* values were reported.

In addition, data from Studies 103 and 104 were pooled for analysis because of the similarity in the study design, population, and treatment regimens. The pre-specified analysis of pooled data facilitated exploration of possible trends in subpopulations and provided more precise estimates of treatment effects for endpoints with fewer events, including reductions in pulmonary exacerbations. The consistency of results across both studies further supported evaluating efficacy based on pooled data. The hierarchical testing procedure was not used for the pooled analyses.

See Section 7.1 through 7.4 for more information about the Phase 3 study designs and methods of analysis.

A total of 1108 patients were dosed in Studies 103 and 104. Approximately 95% of patients completed 24 weeks of treatment. The patients had a mean age of 25 years and a mean baseline ppFEV$_1$ value of 60.6.

Disposition data were similar for the 2 studies and between the LUM600qd/IVA and LUM400q12h/IVA groups (Table 15 on page 62). The pooled FAS included 1108 patients (371 in the placebo group, 368 in the LUM600qd/IVA group, and 369 in the LUM400q12h/IVA group). A high proportion of patients completed treatment (95.1%) and enrolled in extension Study 105 (93.1%).

A higher percentage of patients discontinued treatment in the LUM/IVA groups (5.4% and 6.8%) than in the placebo group (2.4%). The most frequent reason for discontinuation from study drug treatment was an AE. A higher percentage of patients discontinued treatment due to an AE in the LUM/IVA groups than the placebo group (3.8% in LUM600qd/IVA group, 4.6% in LUM400q12h/IVA group, and 1.6% in placebo group).

Demographic and baseline characteristics were similar across the treatment groups in each study and across the 2 studies (see Table 16 on page 63 for individual study results). Table 4 summarizes key demographic and baseline characteristics of pooled Studies 103 and 104.

The study population was taking many chronic standard-of-care CF medications (bronchodilators, dornase alfa, inhaled antibiotics, azithromycin, inhaled hypertonic saline, and inhaled corticosteroids) (Table 17 on page 64 for incidence of medication use). During the studies, patients continued to receive their prescribed therapies for CF, and use of these concomitant medications remained generally stable throughout the treatment period.

Table 4 Demographic and Baseline Characteristics, Pooled Studies 103 and 104, FAS

Characteristic	Placebo N = 371	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Sex: Female, n (%)	181 (48.8)	182 (49.5)	182 (49.3)
Age (years), mean (min, max)	25.4 (12, 64)	24.5 (12, 54)	25.3 (12, 57)
Age group, n (%)			
12 to <18 years	96 (25.9)	96 (26.1)	98 (26.6)
≥18 years	275 (74.1)	272 (73.9)	271 (73.4)
$ppFEV_1$			
Mean (min[a], max)	60.4 (33.9, 99.8)	60.8 (31.1, 92.3)	60.5 (31.3, 96.5)
$ppFEV_1$, n (%)			
<40[a]	28 (7.5)	24 (6.5)	29 (7.9)
≥40 to <70	238 (64.2)	241 (65.5)	233 (63.1)
≥70 to ≤90	97 (26.1)	98 (26.6)	100 (27.1)
>90	3 (0.8)	3 (0.8)	3 (0.8)
BMI (kg/m^2), mean (min, max)	21.0 (14.1, 32.2)	21.0 (14.2, 35.1)	21.5 (14.6, 31.4)

[a] Patients with $ppFEV_1$ <40 at screening were excluded. However, 81 patients (35 patients in Study 103 and 46 patients in Study 104) had $ppFEV_1$ <40 at baseline (range: 31.1 to 39.9). The majority of these patients (96.3%) completed treatment.

See Sections 7.5 and 7.6 for more information about the patient disposition and baseline characteristics.

1.7 Efficacy

In Studies 103 and 104, the primary endpoint was met with high statistical significance for both dosing regimens in both studies.

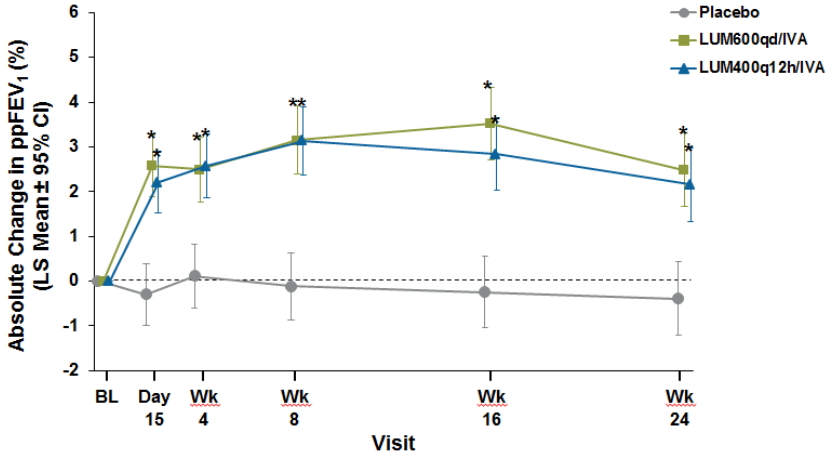
Table 5 Primary Endpoint Results, Studies 103 and 104, FAS

	Study 103		Study 104		Pooled Studies 103 and 104	
Endpoint, Comparison	**LUM600qd/ IVA N = 183**	**LUM400q12 h/ IVA N = 182**	**LUM600qd/ IVA N = 185**	**LUM400q12 h/ IVA N = 187**	**LUM600qd/ IVA N = 368**	**LUM400q12 h/ IVA N = 369**
Absolute change in $ppFEV_1$, treatment difference to placebo (95% CI)	4.0 (2.6, 5.4) *P*<0.0001	2.6 (1.2, 4.0) *P* = 0.0003	2.6 (1.2, 4.1) *P* = 0.0004	3.0 (1.6, 4.4) *P*<0.0001	3.3 (2.3, 4.3) *P*<0.0001	2.8 (1.8, 3.8) *P*<0.0001

Primary endpoint was absolute change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24.

In both studies, improvements in $ppFEV_1$ were rapid in onset, sustained, and consistent (Figure 23 on page 67). The pooled analysis also showed rapid and sustained improvements in $ppFEV_1$ that were consistent between the 2 LUM/IVA regimens (Figure 4).

Figure 4 Absolute Change From Baseline in $ppFEV_1$ Over Time, Pooled Studies 103 and 104, FAS

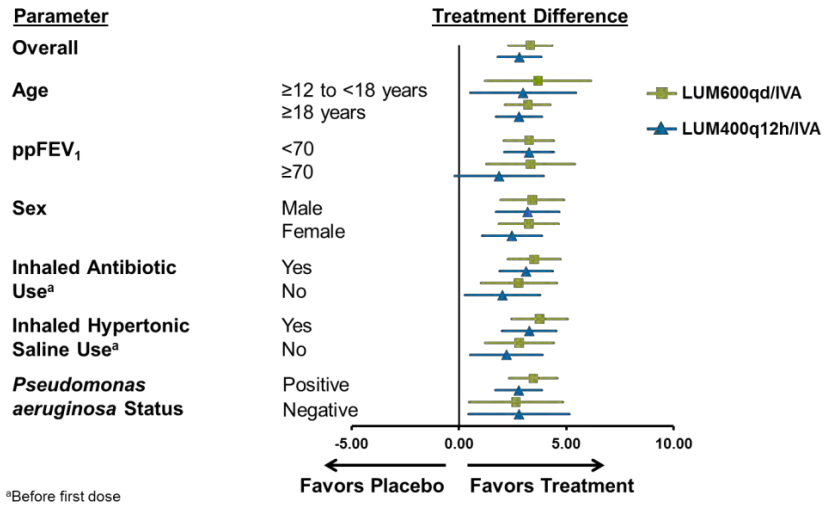


* indicates $P<0.0250$ compared to placebo

	Number of Patients					
	BL	Day 15	Wk 4	Wk 8	Wk 16	Wk 24
Placebo	366	351	353	346	353	350
LUM600qd/IVA	366	349	349	344	345	346
LUM400q12h/IVA	365	356	349	339	344	339

Subgroup analyses of the pooled datasets from Studies 103 and 104 showed consistent efficacy regardless of age, sex, $ppFEV_1$ at Screening, prior use of common CF medications, and *P. aeruginosa* infection (Figure 5).

Figure 5 Subgroup Analyses of Absolute Change in $ppFEV_1$, Pooled Studies 103 and 104, FAS



All key secondary endpoints favored LUM/IVA.

Outcomes favored treatment with LUM/IVA over placebo for all key secondary endpoints: relative change in $ppFEV_1$, change in BMI, change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, patients with ≥5% relative improvement in $ppFEV_1$, and number of pulmonary exacerbations (Table 6). Relative $ppFEV_1$ was statistically significant in both studies, and BMI was statistically significant in Study 104. The testing hierarchy was broken at BMI in Study 103 and CFQ-R respiratory domain in Study 104. Several endpoints were nominally significant ($P \leq 0.0250$, but not considered statistically significant within the framework of the testing hierarchy): CFQ-R respiratory domain for LUM600qd/IVA group in Study 103, patients with ≥5% relative improvement in $ppFEV_1$ for both LUM/IVA groups in both studies, and number of pulmonary exacerbation rate for the LUM400q12h/IVA group in Study 103 and both LUM/IVA groups in Study 104.

In the pooled analysis of Studies 103 and 104, both LUM/IVA regimens resulted in statistically significant improvements in relative change in $ppFEV_1$, patients with relative improvements in $ppFEV_1$ ≥5%, number of pulmonary exacerbations, and change in BMI ($P \leq 0.0250$).

Table 6 Key Secondary Endpoint Results, Studies 103 and 104, FAS

	Study 103		Study 104		Pooled Studies 103 and 104	
Endpoint Comparison	**LUM600qd/ IVA N = 183**	**LUM400q12h/ IVA N = 182**	**LUM600qd/ IVA N = 185**	**LUM400q12h/ IVA N = 187**	**LUM600qd/ IVA N = 368**	**LUM400q12h/ IVA N = 369**
Relative change from baseline in $ppFEV_1$						
Treatment difference to placebo (95% CI)	6.7 (4.3, 9.2) *P*<0.0001	4.3 (1.9, 6.8) *P* = 0.0006	4.4 (1.9, 7.0) *P* = 0.0007	5.3 (2.7, 7.8) *P*<0.0001	5.6 (3.8, 7.3) *P*<0.0001	4.8 (3.0, 6.6) *P*<0.0001
Change from baseline in BMI						
Treatment difference to placebo (95% CI)	0.16 (-0.04, 0.35) *P* = 0.1122	0.13 (-0.07, 0.32) *P* = 0.1938	0.41 (0.23, 0.59) *P*<0.0001	0.36 (0.17, 0.54) *P* = 0.0001	0.28 (0.15, 0.41) *P*<0.0001	0.24 (0.11, 0.37) *P* = 0.0004
Change from baseline in CFQ-R respiratory domain						
Treatment difference to placebo (95% CI)	3.9 (0.7, 7.1) *P* = 0.0168[a]	1.5 (-1.7, 4.7) *P* = 0.3569	2.2 (-0.9, 5.3) *P* = 0.1651	2.9 (-0.3, 6.0) *P* = 0.0736	3.1 (0.8, 5.3) *P* = 0.0071	2.2 (-0.0, 4.5) *P* = 0.0512
Patients with ≥5% relative improvement in $ppFEV_1$						
Odds ratio to placebo (95% CI)	2.94 (1.88, 4.59) *P*<0.0001[a]	2.06 (1.29, 3.28) *P* = 0.0023[a]	2.96 (1.88, 4.64) *P*<0.0001[a]	2.38 (1.52, 3.73) *P* = 0.0001[a]	2.95 (2.15, 4.05) *P*<0.0001	2.22 (1.61, 3.07) *P*<0.0001
Number of pulmonary exacerbations						
Rate ratio to placebo (95% CI)	0.72 (0.52, 1.00) *P* = 0.0491	0.66 (0.47, 0.93) *P* = 0.0169[a]	0.69 (0.52, 0.92) *P* = 0.0116[a]	0.57 (0.42, 0.76) *P* = 0.0002[a]	0.70 (0.56, 0.87) *P* = 0.0014	0.61 (0.49, 0.76) *P*<0.0001

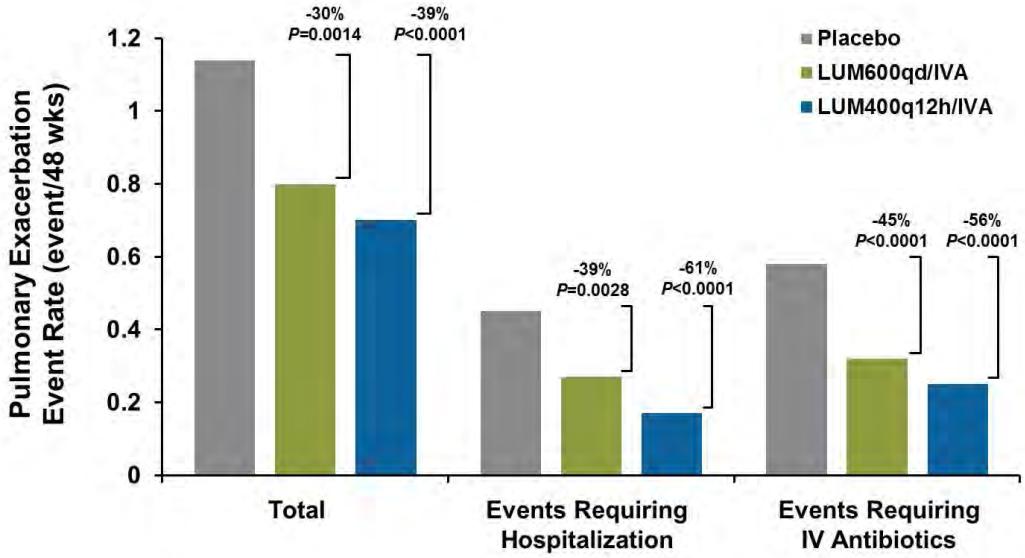
Notes: Within each treatment group for Studies 103 and 104, the treatment difference was considered statistically significant if $P \leq 0.0250$, and if all previous tests within the testing hierarchy also met this level of significance. For the analysis of pooled data from Studies 103 and 104, a testing hierarchy was not applied, and the treatment difference was considered statistically significant if $P \leq 0.0250$.

[a] Endpoint was nominally significant at $P \leq 0.0250$ level; however, it was not considered statistically significant within the framework of the testing hierarchy.

LUM/IVA significantly reduced the rate of pulmonary exacerbations in the pooled analysis, including those requiring hospitalization or intravenous (IV) antibiotics.

Within the individual studies, pulmonary exacerbations were reduced in all 4 LUM/IVA groups with nominally significant *P* values ($P \leq 0.0250$ compared to placebo, but not statistically significant within the framework of the testing hierarchy) for 3 of the 4 dosing groups (Table 6). In the pooled analysis, the reduction in exacerbations was statistically significant in both LUM/IVA dosing regimens compared to placebo. Significant and clinically meaningful reductions in severe pulmonary exacerbations (those requiring hospitalization or use of [IV] antibiotics) were also observed with both LUM/IVA regimens (Figure 6). Greater reductions in overall pulmonary exacerbation rate and severe pulmonary exacerbation rates were observed with the LUM400q12h/IVA regimen.

Figure 6 Reduction in Pulmonary Exacerbation Rates by LUM/IVA, Pooled Studies 103 and 104, FAS



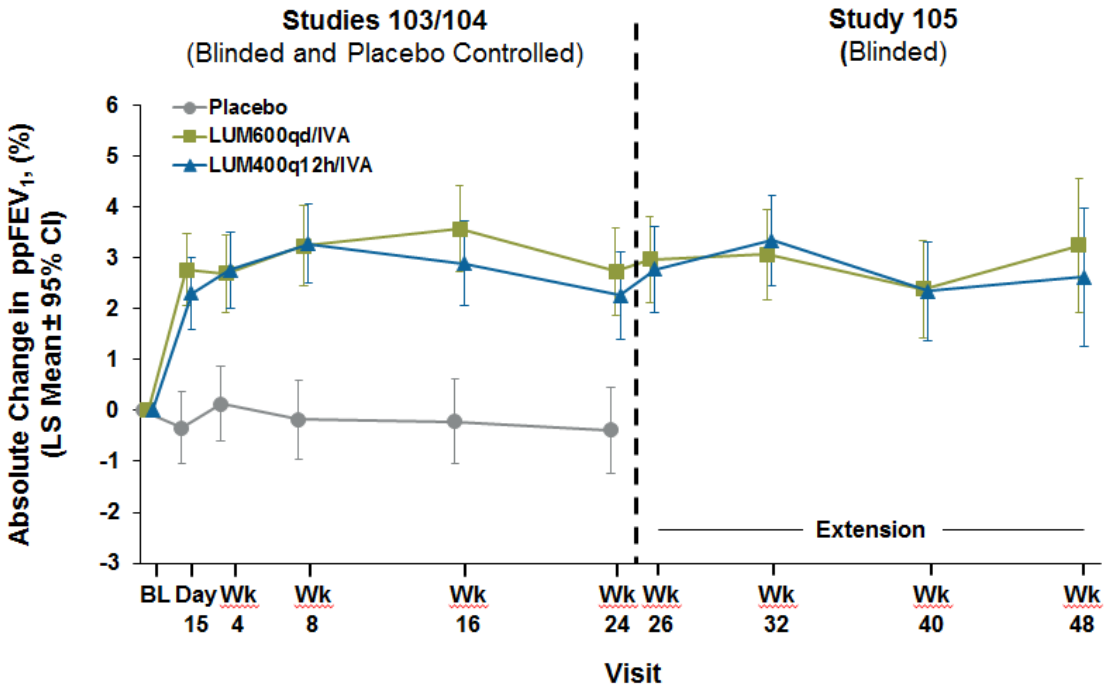
Note: Number of patients in each treatment group: placebo = 371, LUM600qd/IVA = 368, LUM400q12h/IVA = 369.

See Section 7.7 for more information about efficacy results in Studies 103 and 104.

Study 105 interim data showed that improvements in ppFEV$_1$ were sustained through 48 weeks.

An interim analysis of Study 105 was conducted when at least 100 patients had been exposed to LUM/IVA for approximately 48 weeks (in Study 103 or 104 plus Study 105) to provide additional safety data in support of the NDA. Analysis of efficacy included data from 1027 patients who received treatment with LUM/IVA in Study 105 after receiving placebo or LUM/IVA in Study 103 or 104. At the time of the interim analysis, 5.3% patients had discontinued the study. Of the patients who were randomized to the LUM/IVA groups in Study 103 or 104, 604 patients had completed at least the Week 16 Visit, and 194 patients had completed the Week 24 Visit of Study 105. Improvements in ppFEV$_1$ in patients treated with LUM/IVA were sustained for up to 48 weeks for both LUM/IVA regimens (Figure 7).

Figure 7 Durability of ppFEV$_1$ Response, Study 105, FAS



Note: Patients and study site staff were blinded to individual treatment assignment in Studies 103 and 104 and to the dose group in Study 105.

	Number of Patients (Study 105)			
	Day 15	Wk 8	Wk 16	Wk 24
LUM600qd/IVA	319	308	291	95
LUM400q12h/IVA	317	316	283	88

See Section 7.8 for more information about efficacy results in Study 105.

1.8 Safety

The safety profile of LUM/IVA is based on a substantial safety database, including 738 patients with CF treated with LUM/IVA combination therapy in Studies 103 and 104.

The safety population consisted of 1839 people from 17 clinical studies of LUM monotherapy and/or LUM/IVA combination therapy (Appendix 12.2). A total of 1615 people received LUM/IVA combination therapy, including 1349 patients with CF. In Studies 103 and 104, 738 patients were randomized to receive LUM/IVA for 24 weeks (369 patients received LUM600qd/IVA and 369 patients received LUM400q12h/IVA). In Study 105, an additional 353 patients who had received placebo in Study 103 or 104 received LUM/IVA in Study 105.

Data from Studies 103 and 104 were pooled because of the similarity of the study design, population, and treatment regimens in the 2 studies.

See Section 8.2 for more information about the safety population and extent of exposure.

LUM/IVA was generally well tolerated, with a low rate of treatment discontinuation in both LUM/IVA and placebo groups. The safety profiles of the 2 Phase 3 regimens were similar.

Table 7 summarizes the incidence of AEs in Studies 103 and 104. The incidence of serious adverse events (SAEs) was lower in the LUM/IVA group than the placebo group, primarily due to a lower incidence of pulmonary exacerbations among patients in the LUM/IVA groups.

The only SAEs that occurred in at least 0.5% of patients in the total LUM/IVA group and that had a higher incidence than the placebo group included respiratory, elevated liver transaminases, and hepatobiliary events (described below). The frequency of discontinuations due to AEs was low, but was higher in the LUM/IVA group than in the placebo group (4.2% versus 1.6%). The most common AEs (occurred in 3 or more patients) that led to discontinuation were respiratory events, blood creatine phosphokinase increased (CPK), elevated liver transaminases, and hemoptysis (Table 23 on page 80).

Table 7 Summary of Adverse Event Incidence, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
	Placebo	LUM600qd/IVA	LUM400q12h/IVA	Total
	N = 370	N = 369	N = 369	N = 738
Patients With:	n (%)	n (%)	n (%)	n (%)
Any AEs	355 (95.9)	356 (96.5)	351 (95.1)	707 (95.8)
Grade 3 or 4 AEs	59 (15.9)	57 (15.4)	45 (12.2)	102 (13.8)
AEs leading to death	0	0	0	0
SAEs	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
AEs leading to treatment discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)

Note: When summarizing n (%) patients, multiple events were counted only once in that category.

Most AEs in the LUM/IVA group were mild to moderate in severity, did not require treatment discontinuation, and resolved.

The incidence of most AEs was similar across the 2 LUM/IVA treatment regimens (Table 20 on page 78). The most common AE in any treatment group was infective pulmonary exacerbation of CF, a typical manifestation of CF, which occurred at a lower incidence in the total LUM/IVA group (37.5%) than in the placebo group (49.2%) (Table 20 on page 78). Among the AEs with an incidence of at least 10% in any treatment group, cough, sputum increased, and nasal congestion were observed more frequently (at least 3 percentage points) in the placebo group than in the LUM/IVA group (Table 20 on page 78).

AEs for which the incidence in the total LUM/IVA group was ≥5% and was ≥1 percentage point higher than in the placebo group are listed in Table 8.

Table 8 AEs with Incidence ≥5% in Total LUM/IVA Group and ≥1 Percentage Point Higher Than in Placebo Group, Pooled Studies 103 and 104, Safety Set

Adverse Reaction (Preferred Term)	Placebo N = 370 n (%)	LUM/IVA N = 738 n (%)
Dyspnea	29 (7.8)	103 (14.0)
Diarrhea	31 (8.4)	81 (11.0)
Nausea	28 (7.6)	75 (10.2)
Respiration abnormal	22 (5.9)	72 (9.8)
Oropharyngeal pain	30 (8.1)	68 (9.2)
Upper respiratory tract infection	20 (5.4)	61 (8.3)
Rhinitis	18 (4.9)	46 (6.2)
Flatulence	11 (3.0)	44 (6.0)
Rash	7 (1.9)	41 (5.6)
Rhinorrhea	15 (4.1)	38 (5.1)
Vomiting	11 (3.0)	37 (5.0)

See Sections 8.3 and 8.4 for a summary of AEs and SAEs in Studies 103 and 104.

Specific AEs of interest (AESIs) were analyzed by grouping AEs terms that represent similar medical concepts.

Respiratory AEs: Respiratory AEs were more frequent in the total LUM/IVA group than the placebo group; the preferred terms with the highest incidence were dyspnea and respiration abnormal (verbatim term: respiratory chest tightness). In pooled Studies 103 and 104, the incidence of dyspnea was 7.8% in the placebo group and 14.0% in the total LUM/IVA group (LUM600qd/IVA: 14.9%, LUM400q12h/IVA: 13.0%); the incidence of respiration abnormal was 5.9% in the placebo group and 9.8% in the total LUM/IVA group (LUM600qd/IVA: 0.8%, LUM400q12h/IVA: 8.7%).

Approximately three-quarters of the respiratory AEs began during the first week of treatment. Most respiratory AEs were mild or moderate in severity and resolved within 1 to 2 weeks without dosing interruption. After the first week of treatment, respiratory AEs were balanced between the total LUM/IVA group and the placebo group. There were no SAEs of

respiration abnormal and 2 SAEs of dyspnea. Although the etiology is unknown, these respiratory events are likely associated with LUM/IVA. These events led to treatment discontinuation in only 5 (0.7%) LUM/IVA patients in Studies 103 and 104.

See Section 8.6 for a summary of AESIs in Studies 103 and 104.

Liver AEs and Laboratory Values

Liver disease is a known clinical manifestation of CF and is thought to be a result of CFTR dysfunction in biliary tract cells.[32,33] While there is no consensus on the exact definition of CF liver disease, definitions in the literature have included one or more of the following: elevations in transaminases, hepatomegaly, and cirrhosis with or without portal hypertension. CF liver disease has been reported to occur in up to 35% of patients with CF.[34-36]

Elevations in transaminases are common in patients with CF, consistent with the natural history of CF liver disease. In Studies 103 and 104, the incidence of transaminase elevations across several thresholds was similar in the LUM/IVA and placebo groups. In patients exposed to LUM/IVA, there was no apparent relationship between higher exposure to LUM/IVA and the occurrence of transaminase elevations.

Seven LUM/IVA patients had SAEs related to elevated liver enzymes or hepatobiliary disorders compared to no patients in the placebo group. Four of these SAEs were reported as transaminase elevations, 2 as cholestatic hepatitis, and 1 as hepatic encephalopathy. These cases had a range of complex clinical presentations and were all confounded by alternative etiologies and/or risk factors (e.g., hepatitis E seroconversion, CF exacerbation, pre-existing cirrhosis and portal hypertension, prior history of transaminase elevations). All 7 SAEs resolved, and liver function tests returned to baseline for all subjects following resolution. Study drug dosing was discontinued for 4 patients and interrupted for 3 patients. Of the 3 patients for whom study drug was interrupted, study drug dosing was successfully reinitiated for 2 patients. Although the data do not support a causal association between LUM/IVA and these liver events, a contribution cannot be excluded entirely and recommendations for monitoring and management are included in proposed labeling.

Eight patients with pre-existing hepatic cirrhosis and/or portal hypertension were enrolled in the Phase 3 studies. Of these patients, 7 were in the total LUM/IVA group (6 patients in the LUM400q12h/IVA group and 1 patient in the LUM600qd/IVA group) and 1 was in the placebo group. (None of these patients had moderate or severe hepatic impairment by Child-Pugh criteria; no patients with moderate or severe hepatic impairment by Child-Pugh criteria were enrolled in the Phase 3 studies). Among these 8 patients, worsening liver function was observed in 1 patient in the LUM400q12h/IVA group (SAE of increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, and hepatic encephalopathy). The event occurred within 6 days of the start of dosing and resolved following discontinuation of LUM/IVA. As a role for LUM/IVA in this event cannot be excluded, the proposed labeling includes recommendations regarding using LUM/IVA with caution in patients with advanced liver disease and only if the benefits are considered to outweigh the risks. Liver function test monitoring recommendations are included in the proposed labeling.

An interim analysis of the Phase 3 rollover extension study showed a consistent safety profile over 48 weeks of treatment with no new safety signals.

Of the 1054 patients who completed treatment in Study 103 or 104 and thus were eligible to enroll in Study 105, 1050 patients enrolled in Study 105, a long-term safety and efficacy rollover study. A total of 1031 patients enrolled in the treatment cohort, and 19 enrolled in the observational cohort (the observational cohort is not discussed further in this document as these patients did not receive LUM/IVA combination therapy). A subset of patients were included in the Study 105 Long-term Safety Set, which included patients who received active treatment in the previous studies (Studies 103 and 104) and completed visits of Week 24 and beyond in Study 105 as of 01 July 2014. At the time of the data snapshot for the interim analysis, 116 of the patients in the treatment cohort had completed the Week 24 visit in Study 105, of whom 83 had received 48 weeks of LUM/IVA and 116 had received 40 weeks of treatment (Long-term Safety Set).

Safety results during the additional 24 weeks of treatment with LUM/IVA in Study 105 were consistent with those of Studies 103 and 104. The most frequent AE across all treatment groups was infective pulmonary exacerbation of CF.

In patients treated with placebo in Study 103 or 104, mild to moderate early respiratory events were observed when starting LUM/IVA treatment in Study 105, similar to those seen in patients treated with LUM/IVA in Studies 103 and 104.

The incidence of transaminase elevations was low in Study 105 (3.8% >3 × upper limit of normal [ULN], 1.7% > 5 × ULN, and 0.6% >8 × ULN) and similar to that in Studies 103 and 104.

See Section 8.6 for a summary of AESIs in Study 105.

1.9 Recommended Dosage

LUM 400 mg q12h/IVA 250 mg q12h is the recommended dosage regimen.

Improvements in ppFEV$_1$, BMI, and CFQ-R respiratory domain score were similar with both dose regimens evaluated in the Phase 3 studies. The safety profiles of the regimens were also similar. The LUM400q12h/IVA dose regimen yielded greater reductions in pulmonary exacerbations, including those requiring hospitalization or the use of IV antibiotics. This regimen also has potential advantages for patient adherence compared with the LUM600qd/IVA dose regimen because patients can utilize a simple regimen of the same 2 LUM/IVA fixed dose tablets in the morning and the evening compared with the LUM600qd/IVA dose regimen where patients would take 3 LUM/IVA fixed dose tablets in the morning and 2 IVA tablets in the evening. Thus, the LUM400q12h/IVA regimen is recommended for marketing approval.

1.10 Benefit-Risk

LUM/IVA is an example of a precision medicine, specifically designed to treat the underlying cause of disease a well-defined group of patients with a rare, severe condition. LUM/IVA is the first treatment that addresses the underlying cause of CF in people who are homozygous for the *F508del* mutation.

In patients homozygous for *F508del*, LUM/IVA treatment resulted in rapid, consistent, and sustained respiratory and systemic benefits. These clinically meaningful benefits were achieved across multiple clinical endpoints: pulmonary function, pulmonary exacerbations (including those requiring hospitalization or IV antibiotic use), and nutritional measures (BMI and weight). Treatment effects favored LUM/IVA across all subgroups. The effect of LUM/IVA persisted up to 48 weeks and was reproducible in patients who were originally treated with placebo. The benefits of LUM/IVA treatment were seen in addition to receiving their usual CF treatments. Collectively, these results demonstrate the sustained benefits of LUM/IVA treatment and suggest that treating the underlying cause of the disease by modulating CFTR function has the potential to modify the course of disease in patients with CF.

The safety profile of LUM/IVA is well-characterized, with a robust safety database demonstrating a favorable safety profile. The most common AEs associated with LUM/IVA (Table 8) consist of many events typical for CF, and which are recognizable and manageable. Less common risks, which are potentially clinically relevant, including liver function test abnormalities, respiratory events, and DDIs, are well-characterized and readily identified clinically or with routine laboratory monitoring, and potential risks that can be managed through recommendations within the product labeling.

The positive benefit/risk assessment supports approval of LUM/IVA for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

2 DISEASE BACKGROUND AND MEDICAL NEED

Summary

- CF is a progressive, systemic, life-shortening, genetic disease that affects about 30,000 people in the US. CF is caused by defective or missing CFTR protein (an epithelial chloride channel) that results from mutations in the *CFTR* gene.
- Lung disease is the primary cause of morbidity and mortality in people with CF. Pulmonary exacerbations are discrete events that often result in hospitalization and are associated with a more rapid rate of FEV_1 decline. Non-pulmonary aspects of CF also significantly impact the health and quality of life of people with CF.
- Three important goals of CF treatment are to maintain lung function, reduce the frequency of pulmonary exacerbations, and improve nutritional status. With the exception of IVA, currently available treatments for CF target the downstream consequences of the disease.
- IVA is the only approved treatment that targets the underlying cause of CF—the dysfunctional CFTR protein. The population for which IVA is currently approved includes about 1,950 people in the US age 2 years and older who have 1 of 10 specific *CFTR* mutations.
- Results from long-term IVA treatment in patients with the *G551D* mutation (most prevalent mutation for which IVA is approved) show that increasing CFTR function can slow the rate of FEV_1 decline and thus modify the course of disease.
- *F508del* is the most prevalent CF-causing mutation. In the US, about 50% of the total CF population is homozygous for *F508del*. This population has a severe form of CF and a high unmet medical need. LUM/IVA combination therapy has the potential to address the underlying cause of disease in this large segment of the CF patient population.

In this section of the document (Disease Background and Medical Need), the majority of data presented are for the overall CF population. Where available, data are presented for the *F508del* homozygous population, which is the population for the proposed indication for LUM/IVA combination therapy. Patients homozygous for *F508del* comprise about 50% of the overall CF patient population and have a severe form of CF.[30]

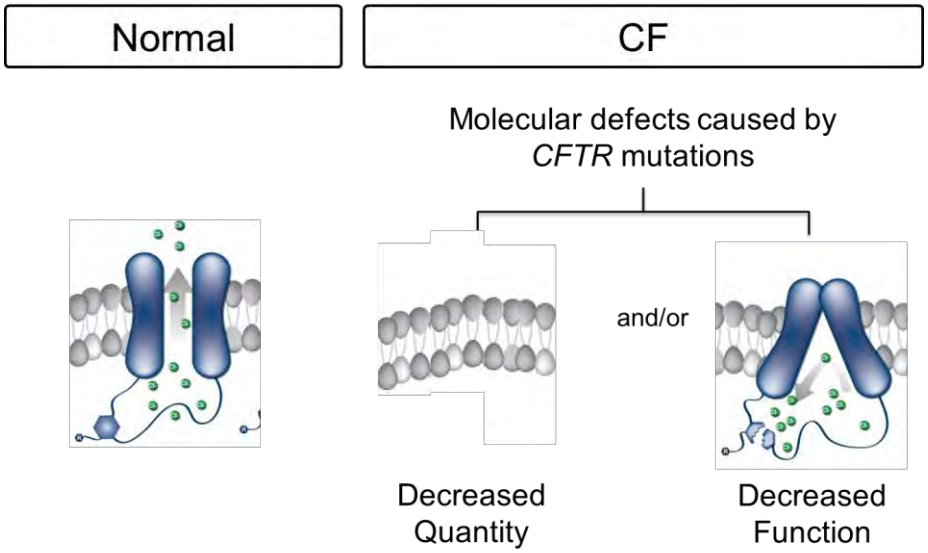
2.1 Overview of Cystic Fibrosis

CF is a progressive, systemic, life-shortening, autosomal recessive disease that affects approximately 30,000 people in the US.[2] CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.[37,38]

Although expected survival has doubled over the past 30 years due to advances in treatment, of those who died in 2013, the median age of death was 27.5 years.[2] A substantial proportion of those who die from CF, die as children.[2] The median predicted age of survival of people with CF who were born in 2013 with CF is 40.7 years of age.[2] In contrast, life expectancy for the general population in 2010 in the US was 74.4 years for non-Hispanic White males and 81.1 years for females.[39]

CF is caused by molecular defects in the CFTR protein that are caused by mutations in the *CFTR* gene. These defects decrease the quantity and/or function of CFTR protein at the cell surface (Figure 8), resulting in decreased CFTR chloride transport.

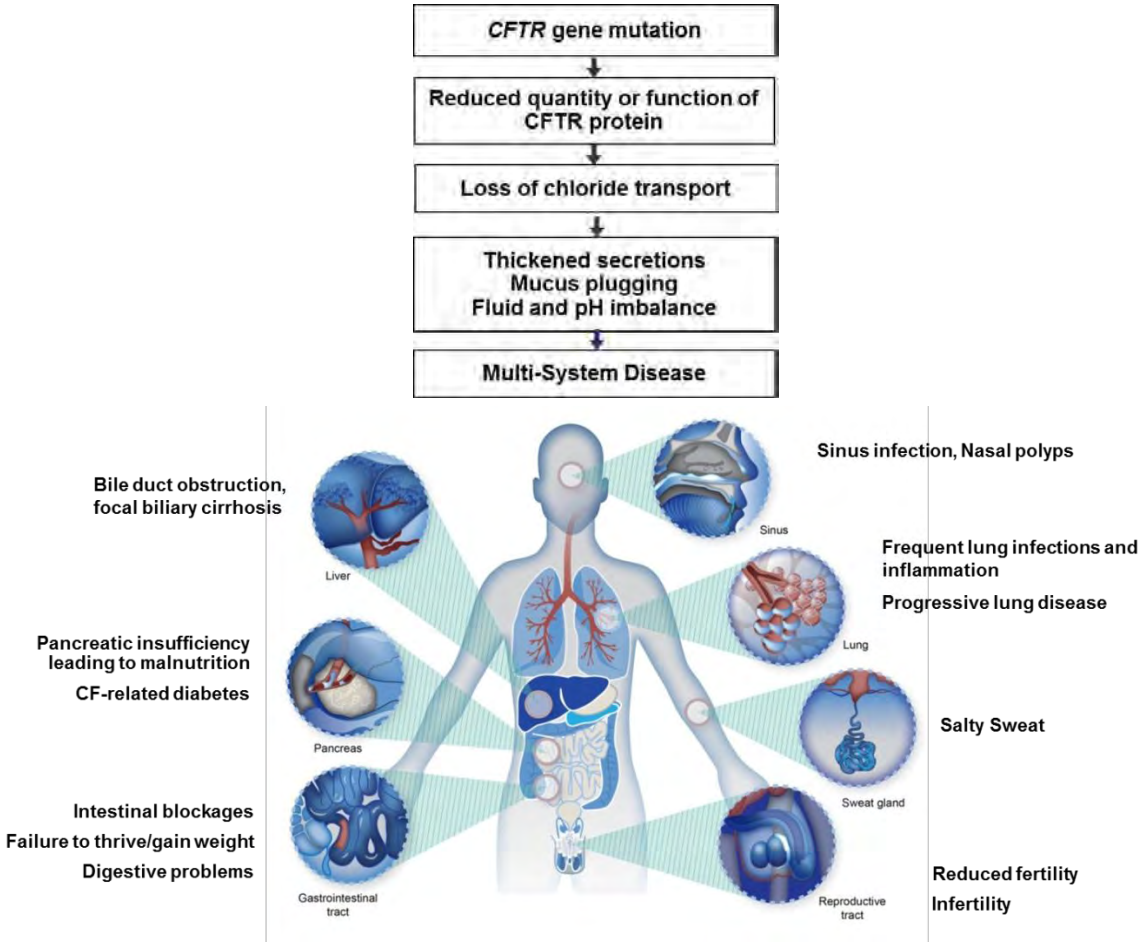
Figure 8 Cystic Fibrosis is Caused by Molecular Defects in CFTR Protein



2.2 Cystic Fibrosis is a Multi-System Disease

The loss of CFTR chloride transport results in the multisystem pathology associated with CF (Figure 9). Lung disease is responsible for most of the morbidity and mortality in CF.[2,3] Chronic lung infection and an exaggerated inflammatory response lead to a progressive, destructive lung disease. There are also a number of gastrointestinal (GI) manifestations including pancreatic insufficiency, intestinal blockage, and failure to absorb adequate nutrients.[3] CF liver disease has been reported to occur in up to 35% of patients with CF, though reports on the prevalence vary widely,[34-36] likely due to the different definitions used, ages studied, and whether the analysis is cross-sectional versus longitudinal.

Figure 9 Pathophysiologic Cascade of CF, a Multi-System Disease



Source: O'Sullivan BP, Freedman SD. Lancet 2009;373:1891-1904.

2.3 Lung Disease

In the lungs, CF results in a cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes and a progressive decline in lung function, and eventually to respiratory failure. Chronic infection with *P. aeruginosa* leads to faster progression of lung disease and a shortened survival.[40,41]

Pulmonary function tests are used to monitor the progression of lung disease. FEV_1 is a strong predictor of mortality in people with CF.[10,14,42] Therefore physicians consider not only acute changes in FEV_1 following intervention, but also whether that response in FEV_1 is sustained over time. With current standard of care, CF patients develop progressive lung disease at an early age. The average rate of lung function decline across the CF population is estimated at 1% to 3% per year.[5]

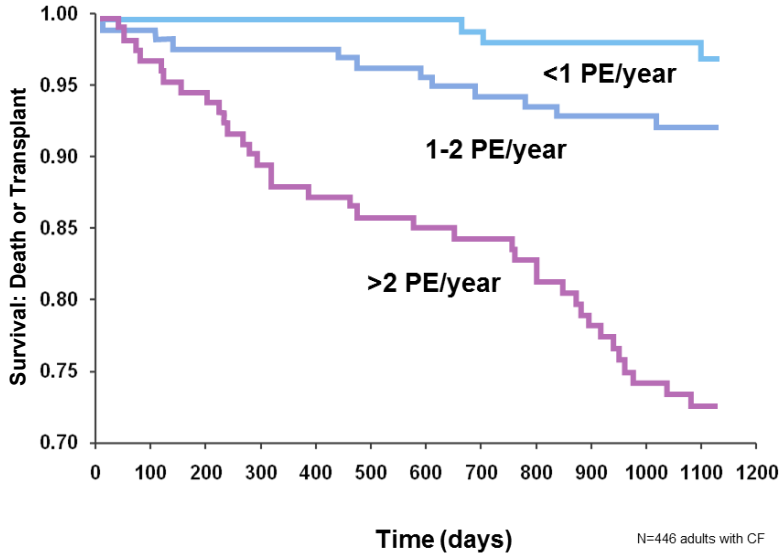
2.4 Pulmonary Exacerbations

The life course of a CF patient is punctuated by acute episodes of pulmonary exacerbations. These events, which often result in hospitalization and absence from school or work, may be life-threatening. Exacerbations are characterized by worsening of respiratory symptoms that are associated with declines in lung function.[43] Patients are typically treated with oral or intravenous (IV) antibiotics and often require hospitalization.[43]

About 25% of exacerbations result in patients failing to recover their baseline lung function after treatment.[44] Even if recovery is achieved, a new lower baseline level of lung function may be established.[6] Exacerbations also result in a faster subsequent rate of decline in FEV_1,[6-8] which then leads to a greater likelihood of future exacerbations. On average, patients 18 years of age and older with 40% predicted FEV_1 have about 1.2 pulmonary exacerbations per year, and this increases to about 1.9 pulmonary exacerbations per year in patients with 20% predicted FEV_1.[45] In the US CF patient population, 35% of patients were treated for a pulmonary exacerbation in 2013, and the mean rate of exacerbations was 0.7/year.[2] Despite advances in treatment, the pulmonary exacerbation rate for the US patient population has not decreased between 2003 and 2013.[2]

Pulmonary exacerbations have been linked to reduced quality of life[46] and increased mortality.[13,44] They have been shown to have a negative impact on survival, with each acute pulmonary exacerbation in a year having an effect equal to subtracting 12 percent from the $ppFEV_1$ value[9,10] (Figure 10).

Figure 10 Kaplan-Meier plot Comparing Time to Death or Lung Transplant Over 3-Year Study Period for Exacerbation Groups



Source: deBoer K et al. Thorax. 2011;66:680-685.

2.5 Nutritional Status

Non-pulmonary aspects of CF significantly impact the health and quality of life of CF patients. Poor somatic growth and poor nutritional status are common due to a number of factors, including increased energy expenditures and appetite suppression due to lung disease; diabetes; and pancreatic insufficiency-related fat malabsorption.[3,11] Even with current therapies, median BMI falls below the CF care goal of the CDC 50th percentile beginning in early adolescence and continues to decrease after that.[2]

One reason for the focus on nutritional measures is the strong association between nutritional status and lung health. An analysis of data from the 2013 US Cystic Fibrosis Foundation (CFF) Registry showed the relationship between $ppFEV_1$ and BMI in adults 20 to 40 years of age.[2] For both males and females, higher BMI was associated with better lung function. Nutritional status has also been shown to be an independent predictor of mortality in people with CF.[12-14]

An analysis conducted by an ad hoc working group of the CFF Subcommittee on Growth and Nutrition using the CFF Patient Registry showed that better FEV_1 status at approximately 80% predicted or above in patients 6 to 20 years of age was associated with BMI percentiles at the 50th percentile and higher.[15] Based on these results, the current CFF practice guidelines recommend that children and adolescents maintain a BMI at or above the 50th percentile. For adults 20 years of age and older, the guidelines recommend a BMI at or above 23 kg/m^2 for men and 22 kg/m^2 for women.[2,15]

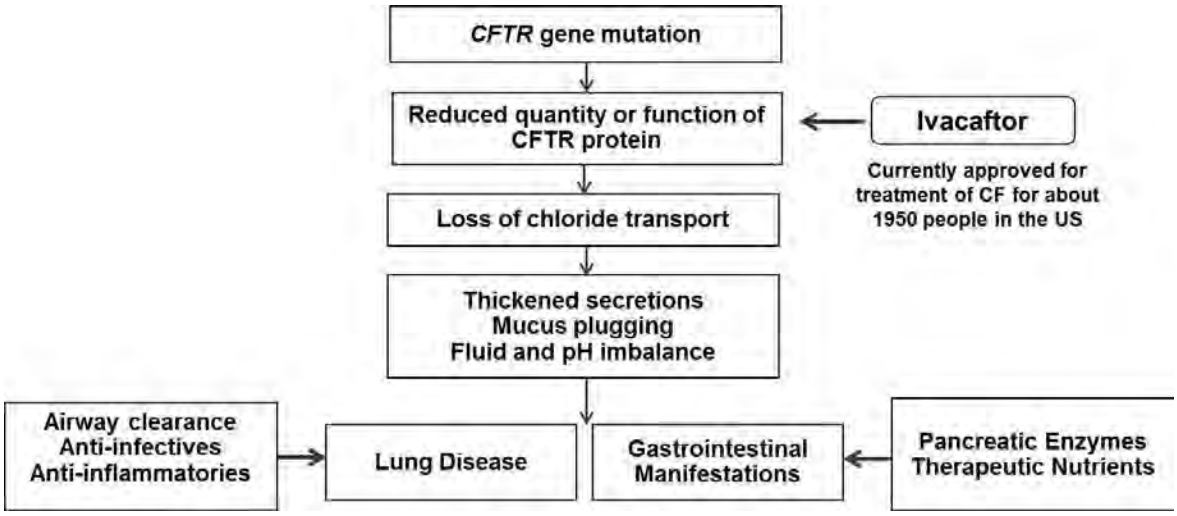
2.6 Treatments for Cystic Fibrosis

Three important goals of CF treatment are to maintain lung function, reduce the frequency of pulmonary exacerbations, and improve nutritional status.

With the exception of IVA, current therapies for CF treat the downstream consequences of disease (Figure 11). Airway obstruction is treated with airway clearance modalities, mucolytics, and bronchodilators. Airway infection and inflammation are targeted with anti-microbial and anti-inflammatory agents. Lung transplantation is a last resort for some patients. Pancreatic insufficiency and malnutrition are addressed with pancreatic enzyme replacement therapy, high caloric diets, and other therapeutic nutrients. The intensive treatment regimen has been reported to take a mean of 74 minutes per day by children between 10 and 16 years of age[47] and 108 minutes per day by adults.[48]

IVA is the only approved treatment that targets the underlying cause of CF—the dysfunctional CFTR protein. In the US, IVA (KALYDECO) is approved for the treatment of CF in patients age 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *R117H*. This population includes about 1,950 people in the US.

Figure 11 Current Therapies for Majority of CF Patient Population Target the Downstream Manifestations of CF



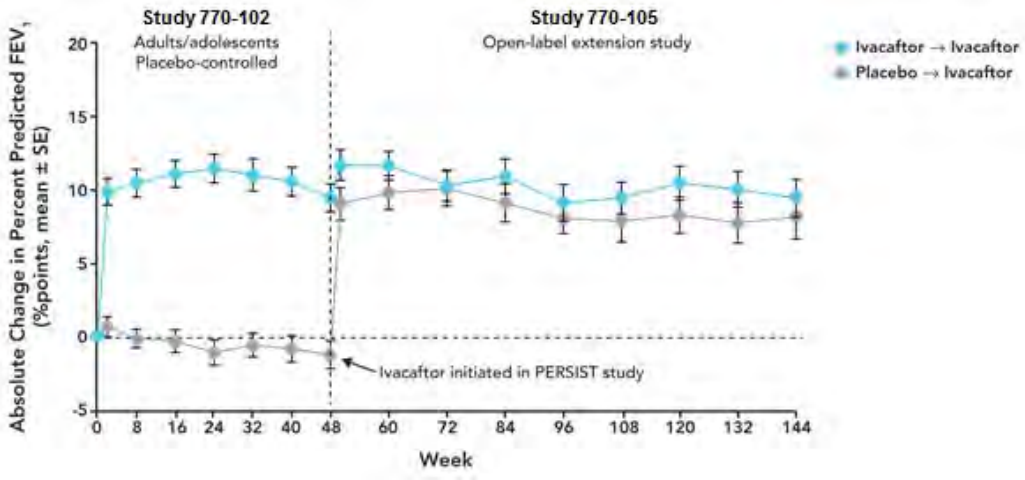
Source: Ratjen. Respir Care. 2009; 54:595-605; Jones et al. Drugs. 2009; 69:1903-10; Davis et al., Am J Respir Crit Care Med. 1996; 154: 1229-56.

By targeting the defective CFTR protein, LUM/IVA combination therapy provides an opportunity to treat the underlying cause of CF in people homozygous for *F508del*.

2.7 Evidence That CFTR Modulation Can Change the Course of Disease

Changes in $ppFEV_1$ in people with the *G551D-CFTR* mutation (most prevalent mutation for which IVA is approved) treated with IVA illustrate both the rapid increase in $ppFEV_1$ after the start of treatment and the sustained benefit of treatment (Figure 12).

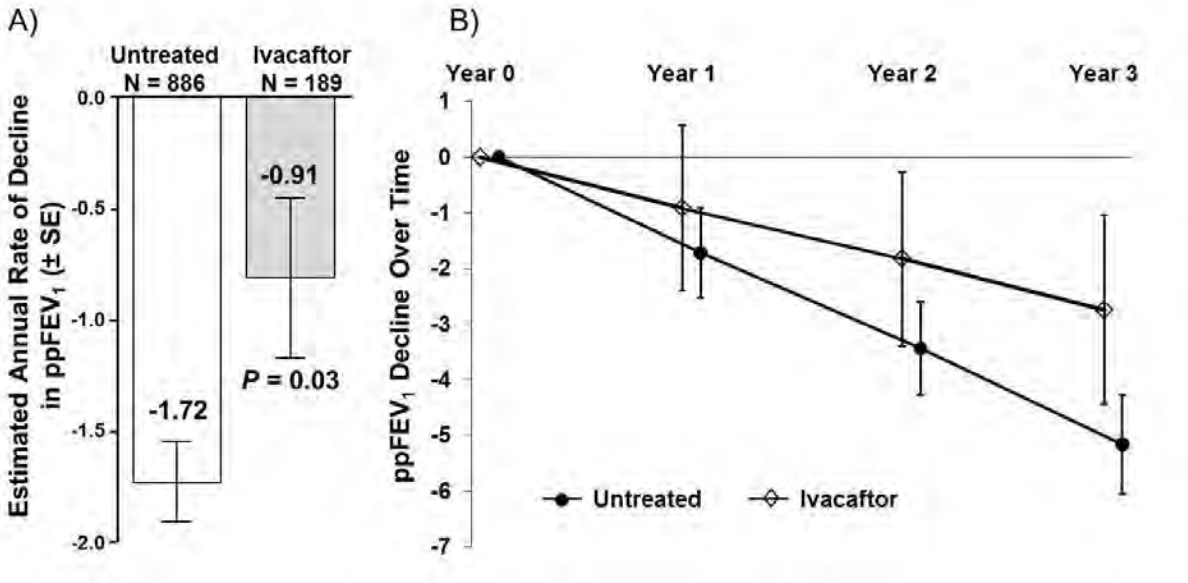
Figure 12 Studies 770-102 and 770-105: Mean Absolute Change From Baseline in Percent Predicted FEV_1 for Patients 12 Years of Age and Older with the *G551D-CFTR* Mutation



Source: McKone E et al. Lancet Respir Med. 2014;2(11):902-10.
Observed (raw) mean changes are plotted. Changes are measured from baseline of Study 770-102.

Further analysis of the data showed that IVA reduced the slope of $ppFEV_1$ by about 50% compared to an untreated homozygous *F508del* control population from the US CFF registry (Figure 13A). These results demonstrate the sustained benefits of IVA treatment and suggest that modulating CFTR can modify the course of disease in patients with CF. Figure 13B shows the effect on the projected FEV_1 decline over the 3 year period.

Figure 13 Ivacaftor Reduces the Rate of Lung Function Decline in Patients with *G551D* Mutation



Source: Modified from Sawicki G, McKone E, Pasta D, et al. The Effect of Ivacaftor on the Rate of Lung Function Decline in CF Patients With a G551D-CFTR Mutation. Presented at the 37th Meeting of the European Cystic Fibrosis Society at Gothenburg, Sweden, 12 June 2014. Data on file.

2.8 F508del Homozygous: Clinical Phenotype

F508del is the most common CF-causing mutation. In the US, about 50% of the total CF population is homozygous for *F508del*,[2,25] including about 8,500 people age 12 years and older. *F508del* causes a severe defect in the processing and trafficking of CFTR, resulting in little-to-no CFTR protein at the cell surface.[18-24] Because of the near-complete loss of CFTR chloride transport, the *F508del/F508del* mutation is typically associated with a severe form of CF, characterized by a rapid rate of lung function decline, colonization with *P. aeruginosa*, a high incidence of pancreatic insufficiency, and reduced life expectancy.[26 -29]

3 MECHANISM OF ACTION AND IN VITRO RESULTS

- *F508del* causes a severe defect in CFTR protein processing and trafficking that prevents most of the CFTR protein from reaching cell surface.
- LUM and IVA in combination treat the underlying molecular defect and enhance the overall function of CFTR in people homozygous for *F508del*:
  - LUM is a CFTR corrector that acts directly on F508del-CFTR to improve its processing and trafficking, thereby increasing the quantity of functional CFTR at the cell surface.
  - IVA is a CFTR potentiator that increases the channel open probability (channel gating) of F508del-CFTR delivered to the cell surface by LUM. In the absence of LUM, IVA has minimal effect on chloride transport in F508del-HBE because there is little-to-no F508del-CFTR protein at the cell surface.
  - The combined effect of LUM and IVA is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride transport.
- Nonclinical data showed that the improvement in F508del-CFTR chloride transport provided by LUM in combination with IVA was superior to that of either LUM or IVA alone.
- The mechanism of action of LUM and IVA and results of in vitro studies supported development of LUM/IVA combination therapy for the treatment of CF in patients homozygous for *F508del*.

3.1 Modulation of CFTR

The type and severity of the molecular defects caused by different CF-causing *CFTR* mutations are well understood based on biochemical and electrophysiological studies.[18-24] The molecular defects result in decreased quantity of CFTR on the cell surface and/or reduced function of the CFTR protein, which leads to decreased CFTR chloride transport.

Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. The first approach is to increase the quantity of CFTR delivered to the cell surface using small molecules known as CFTR correctors (e.g., LUM). The second approach is to increase the channel gating activity of CFTR at the cell surface using small molecules known as CFTR potentiators (e.g., IVA).

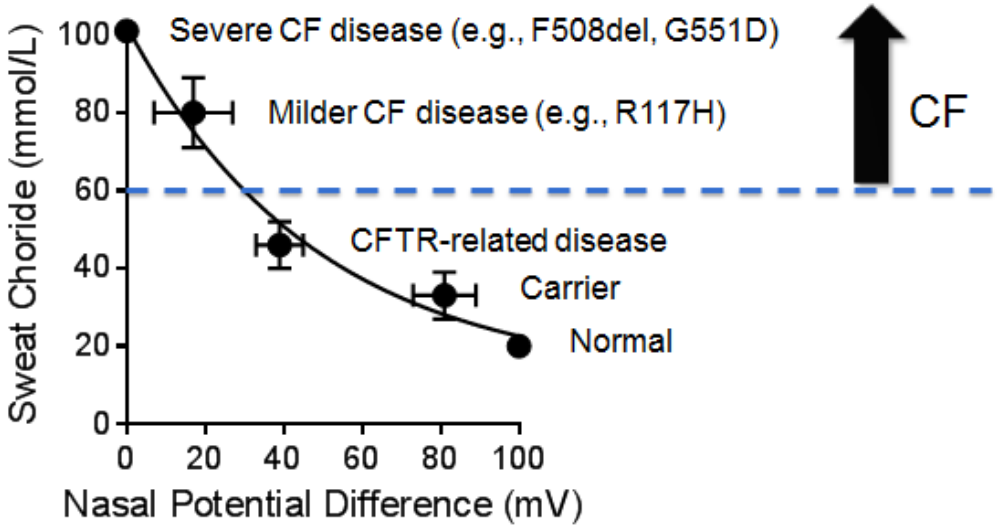
One or both of these mechanisms may be necessary depending on the specific mutation. Because the channel gating activity of CFTR delivered to the cell surface by CFTR correctors can be enhanced by CFTR potentiators, together, CFTR correctors and potentiators provide complementary therapeutic approaches to improve chloride transport.

3.2 Genotype-Phenotype Correlation in CF

Approximately 2000 mutations in the *CFTR* gene have been identified,[49] and more than 150 of those are known to be disease-causing.[25] These mutations result in decreased quantity of CFTR on the cell surface and/or reduced function of the CFTR protein at the cell surface, which leads to decreased CFTR chloride transport.

Natural history studies established that the relationship between disease phenotype (severity and rate of progression) generally correlates with the extent of loss of chloride transport (Figure 14). A complete or near complete loss of CFTR-mediated chloride transport results in CF characterized by an early onset and relatively rapid disease progression. Data from natural history studies suggest that a 10% to 20% improvement in CFTR function results in clinical benefit (Figure 14).

Figure 14 Level of CFTR Dysfunction Relates to Disease Phenotype



Source: Strausbaugh, Clin Chest Med 2007,28: 279–88; McKone et al, Chest 2006,130:1441-7; McKone et al, Lancet 2003, 361: 1671-6; Noone et al. Gastroenterology 2001;121:1310–9; Noone et al. Am J Respir Crit Care Med. 2000;162:1919–24; Davis et al. Am J Respir Crit Care Med. 1996; 154:1229-56.
Note: Nasal potential difference is a measure of CFTR activity

Although there is phenotypic variability in clinical phenotype and disease progression between genotypes and even between patients with the same genotype (due to contributions from modifier genes and environmental factors), certain genotypes, most notably *F508del* homozygous are associated with severe clinical disease with an early onset of progressive lung disease, high sweat chloride concentrations, and pancreatic insufficiency.

3.3 *F508del* Mutation and Complimentary Mechanisms of Action of LUM and IVA

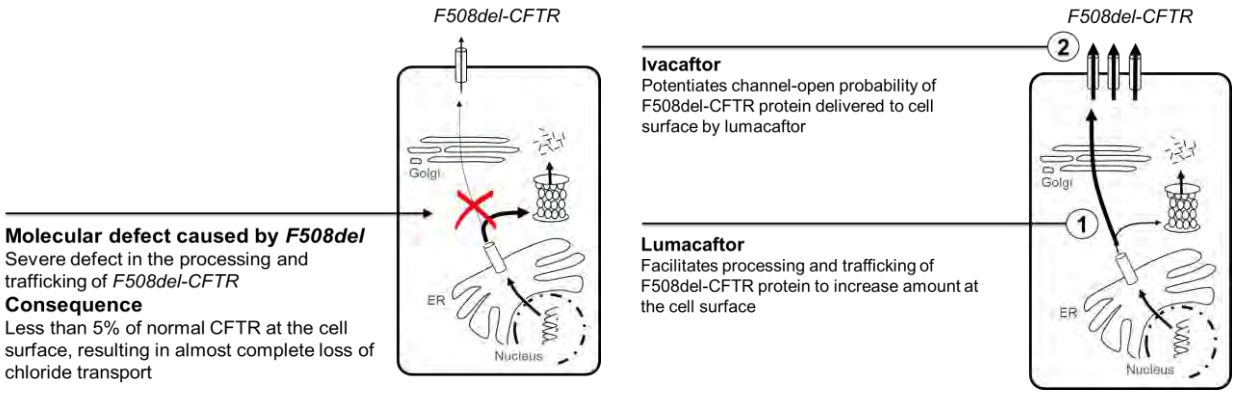
The vast majority of *CFTR* mutations are rare. However, *F508del* has a prevalence of about 90% in the overall CF patient population, and about 50% of people in the US with CF are *F508del* homozygous.

F508del is an in-frame deletion in the *CFTR* gene that results in a loss of phenylalanine at position 508 in the CFTR protein.[50] The molecular defects caused by *F508del* are well-understood. *F508del* causes a severe defect in the processing and trafficking of CFTR, resulting in little-to-no CFTR protein at the cell surface (Figure 15A).[18-24]

Lack of CFTR protein at the cell surface results in the almost complete loss of chloride transport, which causes severe manifestations of CF-related disease in patients who are *F508del* homozygous. In addition, the very small amount of F508del-CFTR protein that reaches the cell surface has defective channel gating and decreased stability.[51]

LUM and IVA in combination treat the underlying molecular defect and enhance the function of CFTR in people homozygous for *F508del*. The combined effect of LUM and IVA is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride transport (Figure 15B).

Figure 15 *F508del*: Molecular Defect and LUM/IVA Mechanisms of Action on F508del-CFTR



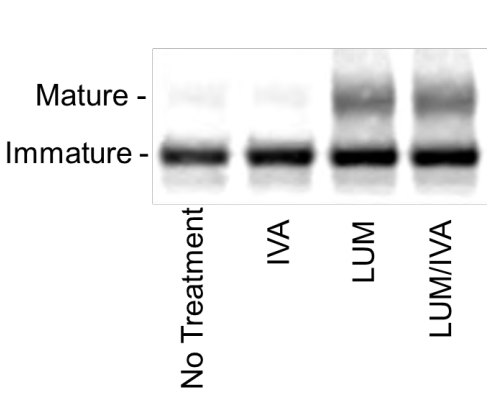
3.4 LUM and IVA: Effects on F508del-CFTR Protein In Vitro

The improvement in the processing and trafficking of F508del-CFTR in response to LUM and IVA was quantified in immunoblot studies using cultured *F508del/F508del*-HBE. The exit of F508del-CFTR from the endoplasmic reticulum and passage through the Golgi (cellular trafficking) is characterized by an increase in the molecular weight of the CFTR protein from a 135–140 kDA band (immature CFTR) to a 170-180 kDA band (mature CFTR) due to glycosylation (processing) of the protein in the Golgi. Because *F508del* affects the processing and trafficking of the protein, in the absence of treatment, very little mature protein is produced (Figure 16, lane 1).

LUM facilitates the processing and trafficking of the F508del-CFTR protein, leading to an increase in the quantity of functional CFTR at the cell surface (Figure 16). By this mechanism, LUM addresses the underlying molecular defect in CFTR caused by the *F508del-CFTR* mutation.

IVA does not improve the processing and trafficking of F508del-CFTR (Figure 16). However, IVA potentiates the channel open probability (channel gating) of the F508del-CFTR delivered to the cell surface by LUM. In the presence of LUM alone, the open probability of F508del-CFTR was 0.23±0.02. This doubled to 0.52±0.04 in the presence of IVA, an open probability that is approximately normal (open probability of normal CFTR is 0.47±0.04).

Figure 16 Processing and Trafficking of F508del-CFTR Protein in *F508del/F508del*-HBE Treated with IVA, LUM, or LUM/IVA



Lane 1: Glycosylation pattern of F508del-CFTR from vehicle-treated *F508del/F08del*-HBE cell lysates. CFTR in the endoplasmic reticulum (immature CFTR or band B) is characterized by a 135 to 140 kDa band.
Lanes 2, 3, and 4: Glycosylation pattern of F508del-CFTR following pre-treatment of *F508del/F08del*-HBE for 24 hours with 0.1 µM IVA, 3 µM LUM, or 3 µM LUM + 0.1 µM IVA. Lanes 3 and 4 show the appearance of CFTR that has undergone processing by the golgi (mature CFTR or band C; characterized by a 170 to 180 kDa band).

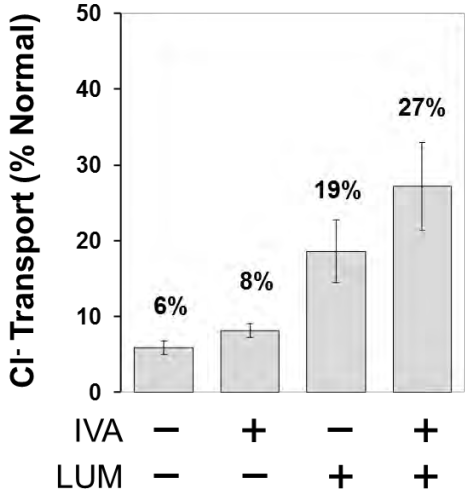
In studies of LUM/IVA treatment of *F508del/F508del*-HBE, the LUM EC_{50} was 81 ± 19 nM and the IVA EC_{50} was 2 nM (this is 10-fold lower than the 20 nM EC_{50} value for *G551D*, one of the mutations approved for IVA monotherapy).

3.5 LUM and IVA: Effects on F508del-CFTR Chloride Transport

Nonclinical studies were conducted to quantitate the contribution of LUM and IVA to improvement in F508del-CFTR chloride transport (Figure 17).

- Primary cultures of F508del/F508del-HBE had only 6% of normal CFTR chloride transport in the absence of LUM or IVA, consistent with the presence of little-to-no F508del-CFTR protein at the cell surface.
- IVA alone enhanced chloride transport to 8% of normal CFTR. This minimal increase in chloride transport was expected based on the molecular defect caused by the *F508del-CFTR* mutation and the mechanism of action for IVA because there is not a sufficient quantity of CFTR present at the cell surface for IVA to work.
- LUM alone enhanced chloride transport to 19% of normal CFTR. These findings are consistent with the mechanism of action of LUM, which facilitates the processing and trafficking of F508del-CFTR to increase the quantity of functional F508del-CFTR at the cell surface.
- The combination of LUM and IVA enhanced chloride transport to 27% of normal CFTR. This magnitude of increase, compared to that with LUM or IVA alone, is due to the complimentary mechanisms of action of these two drugs: LUM increases the quantity of F508del-CFTR protein on the cell surface, and IVA increases the open probability of that protein. The result is a greater increase in chloride transport than that achieved with either drug alone.

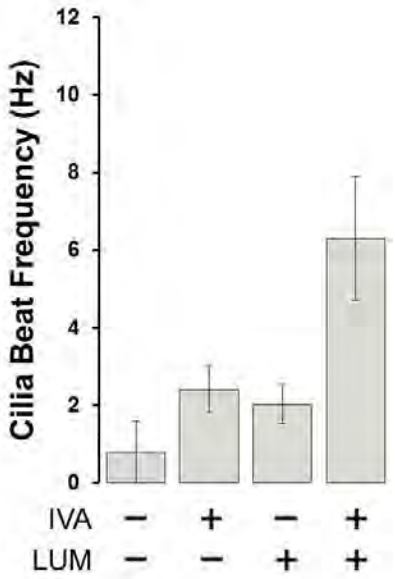
Figure 17 CFTR Chloride Transport in F508del/F508del-HBE Cells Treated With IVA, LUM, or LUM/IVA



Note: Ussing chamber recordings of the 10 μM forskolin-stimulated chloride transport in *F508del/F508del*-HBE cells derived from a 4 donor bronchi treated for 24 hours with vehicle, 0.1 μM IVA, 3 μM LUM, or 3 μM LUM and 0.1 μM IVA. Data are mean (± SEM) values from the 4 donor bronchi.

In vitro, restoration of chloride transport through the action of the combination of LUM and IVA improved fluid regulation and cilia beat frequency. Co-treatment of primary cultures of *F508del/F508del*-HBE cells with LUM and IVA for 72 hours significantly increased both the airway surface liquid height and cilia beat frequency compared to vehicle-treated controls or compared with either drug alone (Figure 18). In people with CF, this would be expected to improve mucociliary clearance, consistent with the ability of LUM/IVA combination therapy to address the underlying pathogenesis of CF.

Figure 18 Cilia Beat Frequency in F508del/F508del-HBE Cells Treated With IVA, LUM, or LUM/IVA



Effect of 72-hour treatment with 3 µM IVA, 3 µM LUM, or the combination on cilia beat frequency in *F508del/F508del*-HBE cells derived from 5 donor bronchi (mean ± SEM; n = 5 donors, 1 to 3 replicates per donor).

4 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM AND REGULATORY INPUT

Vertex began the clinical development of LUM in the US in 2007 and subsequently expanded the development to include the EU, Canada, and Australia.

The development program includes 15 completed studies and 2 ongoing studies (See Appendix 12.2 for a list of studies). The studies evaluated LUM monotherapy and/or LUM/IVA combination therapy in healthy subjects and in patients with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Studies were also conducted in subjects with hepatic impairment and patients with CF who are pancreatic insufficient.

Studies in patients with CF were developed with consultation from the US Cystic Fibrosis Foundation (CFF), the CFF Therapeutics Development Network (TDN), the European Cystic Fibrosis Society (ECFS) Clinical Trials Network (CTN), and regulatory agencies.

US Fast Track (17 January 2008), Orphan (02 March 2010; plus joint LUM/IVA designation 30 June 2014), and Breakthrough designations (07 December 2012) were subsequently granted by the FDA to LUM.

Regulatory advice on the clinical development plan and the designs for Studies 103 and 104 was sought from regulatory authorities in the US and EU; regulatory agencies agreed with the final proposed study designs. The study designs, including the treatment duration of 24 weeks, were developed in accordance with the Committee for Medicinal Products for Human Use Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis,[52] Guidances for Chronic Obstructive Pulmonary Disease,[53,54] ICH Topic E11,[55] and precedent from other drugs approved for CF.[31,56,57] Vertex also sought FDA and external expert advice on the statistical analysis plans for Studies 103 and 104 during Phase 3, before database lock and treatment unblinding.

According to regulatory guidelines, change in ppFEV$_1$ is the recommended primary clinical endpoint in efficacy studies for CF[52] (and chronic obstructive pulmonary disease[53,52]). Because the LUM/IVA combination is a systemic therapy that targets the underlying defect in CF, the pivotal Phase 3 studies (Studies 103 and 104) were designed to evaluate lung function (FEV$_1$), respiratory symptoms, pulmonary exacerbations, and nutritional effects (weight and BMI).

Under the US Breakthrough Designation, Vertex continuously received constructive guidance from the Agency throughout LUM/IVA development in the *F508*del homozygous population, up to and including the pre-NDA meeting on 12 August 2014, and during review of the NDA to date.

The NDA was received by the FDA on 05 November 2014, and FDA granted Priority Review status with a filing date of 04 January 2015. An Advisory Committee Meeting with Pulmonary-Allergy Drugs Advisory Committee was scheduled to discuss this application.

5 PHASE 2 PROGRAM

Summary

- The Phase 2 program in people homozygous for *F508del* was designed to (1) determine if the combination of LUM and IVA is more effective than either drug alone, (2) evaluate the safety profile of the selected therapy to further assess in Phase 3 studies, and (3) determine the dose for Phase 3 studies.
- IVA monotherapy was not effective in patients homozygous for *F508del.*
- LUM monotherapy decreased sweat chloride but did not increase $ppFEV_1$ in patients homozygous for *F508del.*
- The improvements in F508del-CFTR function demonstrated in vitro translated to sweat chloride response in CF patients homozygous for *F508del* and confirmed that superior improvement was provided by the combination of LUM and IVA compared to either drug alone.
- Consistent with the sweat chloride results, improvements in $ppFEV_1$ were observed with LUM/IVA combination therapy, confirming that the combination is superior across in vitro, PD, and clinical endpoints.
- The incidence of AEs was similar between the LUM/IVA and placebo groups. The majority of AEs were mild or moderate in severity and were consistent with the expected manifestations of CF disease. There were no consistent clinically important trends attributable to LUM/IVA identified in clinical laboratory results.
- An IVA dosage of 250 mg q12h was selected for use in the combination regimens (instead of the approved monotherapy dosage of 150 mg q12h) because LUM is a strong CYP3A inducer and IVA is a sensitive CYP3A substrate.
- The LUM600qd/IVA and LUM400q12h/IVA regimens were included in the Phase 3 studies because they both provided evidence of efficacy and safety.

5.1 Direct Measure of CFTR Function (Sweat Chloride)

Extensive data from natural history studies indicate that improving CFTR function in patients homozygous for the *F508del-CFTR* mutation by 10% to 20% would be expected to result in meaningful clinical benefit.[50-64] This, together with the understanding of the molecular defect caused by the *F508del* mutation and the magnitude of improvement in F508del-CFTR function observed in vitro and in vivo, led to the expectation that the combination of LUM and IVA would provide superior clinical benefit compared to either drug alone. Results of Phase 2 studies confirmed these expectations.

Phase 2 studies evaluated IVA monotherapy, LUM monotherapy, and LUM/IVA combination therapy in patients homozygous for *F508del*. These studies included assessments of sweat chloride concentrations and lung function ($ppFEV_1$). Sweat chloride is a direct in vivo measure of CFTR function in the sweat gland. Consistent with the lack of *F508del-CFTR* at the cell surface, the average sweat chloride level in the population of patients homozygous for *F508del* is 103 mmol/L.[25] This is elevated compared to the

60 mmol/L threshold for diagnosis of CF. A reduction in sweat chloride indicates enhanced CFTR function in vivo.

5.1.1 IVA Monotherapy

Before the Phase 2 study evaluating LUM monotherapy and LUM/IVA combination therapy was initiated (Study 102), a placebo-controlled Phase 2 study was conducted to evaluate IVA monotherapy in patients homozygous for *F508del* (Study 770-104). IVA monotherapy (150 mg q12h) resulted in minimal change in sweat chloride, and the study did not meet the primary efficacy endpoint (absolute change in $ppFEV_1$ from baseline through Week 16) or any other efficacy endpoints (Table 9). These results are consistent with the very small effect of IVA observed in vitro (Section 3).

Treatment effects on relative change in $ppFEV_1$, pulmonary exacerbations, and CFQ-R respiratory domain were not statistically significant (Table 9). The effect on BMI favored the placebo group. Furthermore, in the IVA monotherapy group, the within-group effect on CFQ-R respiratory domain (change from baseline to end of treatment) was negative.

Overall, the negative study outcome is to be expected based on the mechanistic understanding of the underlying defect in *F508del-CFTR* mutation, the minimal in vitro effects of IVA alone on chloride transport in *F508del/F508del*-HBE cells, and the minimal improvements in sweat chloride in Study 770-104.

Table 9 IVA Monotherapy: Summary of Clinical Results in Patients Homozygous for *F508del*, Study 770-104

Endpoint	Treatment Difference (95% CI)	*P*-Value
Average change in sweat chloride (mmol/L)	-2.9 (-5.6, -0.2)	0.04
Average absolute change in $ppFEV_1$ (percentage points)	1.72 (-0.63, 4.08)	0.1509
Change in BMI (kg/m^2)	-0.07 (-0.36, 0.23)	0.6655
Average absolute change in CFQ-R respiratory domain score	1.31 (-2.92, 5.55)	0.5408
	Rate Ratio (95% CI)	***P*-Value**
Number of pulmonary exacerbations	0.677 (0.334, 1.372)	0.2795

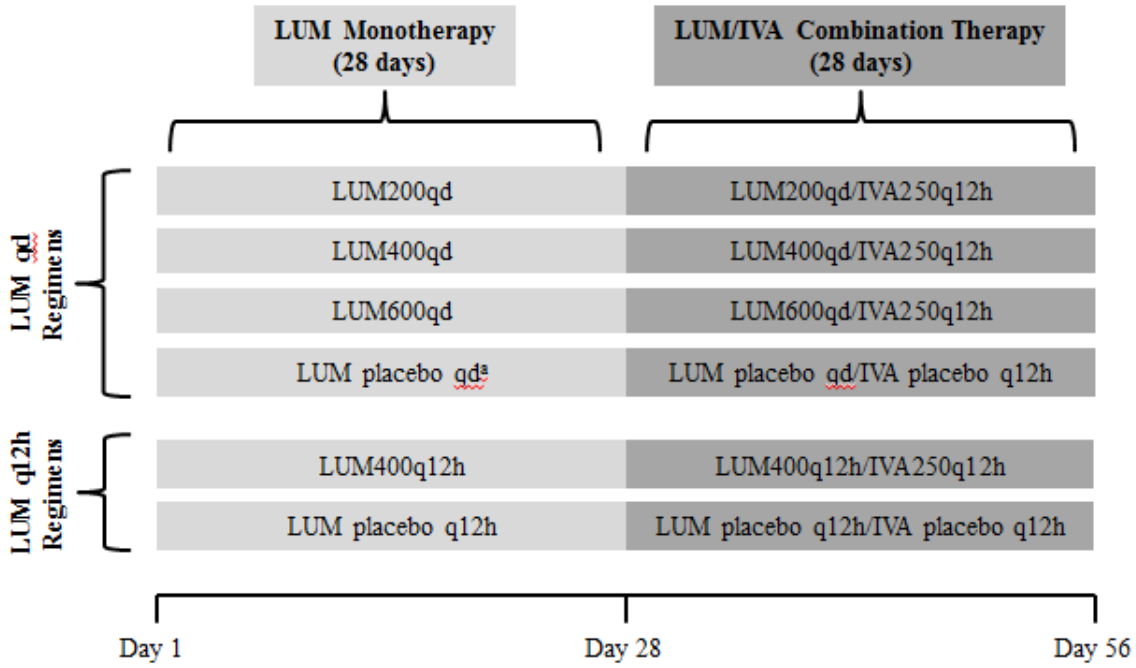
IVA dosage was 150 mg q12h (recommended dosage for approved indications with IVA monotherapy)

5.1.2 LUM Monotherapy

Study 101 was a Phase 2 dose-ranging study evaluating LUM monotherapy for 28 days in patients with CF who are homozygous for *F508del*. Study101 did not provide a clinically meaningful benefit, but resulted in significant reduction in sweat chloride (data not shown).

Study 102 was a Phase 2, placebo-controlled, parallel-group, multi-cohort study that evaluated LUM monotherapy and LUM/IVA combination therapy in CF patients homozygous for *F508del*. Each patient received LUM monotherapy for up to 28 days, immediately followed by LUM/IVA combination therapy for up to 28 days. The same doses of LUM (200 mg to 600 mg daily or 400 mg q12h) were evaluated during monotherapy and combination therapy. A dose of 150 mg q12h or 250 mg q12h of IVA was evaluated during the combination therapy. Figure 19 shows the longest duration of LUM monotherapy and LUM/IVA combination therapy evaluated in Study 102.

Figure 19 Schematic of Longest Duration of Treatments Evaluated in Study 102



[a] CF patients homozygous and heterozygous for *F508del* were included in this group.

Treatment with LUM monotherapy decreased sweat chloride concentrations, with the largest changes observed for the 3 highest doses (Table 10). LUM400q12h led to a change in sweat chloride of -8.2 mmol/L compared with placebo and LUM600qd led to a change in sweat chloride of -6.1 mmol/L compared with placebo. Overall, the decreased in sweat chloride concentrations observed with LUM monotherapy is consistent with the mechanism of action of LUM and the in vitro data showing that LUM increases the quantity of functional F508del-CFTR at the cell surface (Section 3.4). However, LUM monotherapy was unexpectedly associated with a dose-dependent decline in $ppFEV_1$ (Table 10).

Table 10 Sweat Chloride and $ppFEV_1$ Assessments at Day 28 (End of LUM Monotherapy Dosing), Study 102

Endpoint	LUM200qd N = 21	LUM400qd N = 20	LUM600qd N = 20	LUM400q12h N = 11
Sweat chloride: Change from baseline at Day 28				
Treatment difference versus placebo (95% CI)	-4.9 (-9.5, -0.3) *P* = 0.038	-8.3 (-13.0, -3.6) *P*<0.001	-6.1 (-10.8, -1.4) *P* = 0.012	-8.2 (-14.1, -2.3) *P* = 0.007
Absolute change in $ppFEV_1$: Change from baseline at Day 28				
Treatment difference versus placebo (95% CI)	0.2 (-3.7, 4.2) *P* = 0.904	-1.4 (-5.4, 2.6) *P* = 0.497	-2.7 (-6.7, 1.4) *P* = 0.196	-4.6 (-9.6, 0.4) *P* = 0.069

5.1.3 LUM/IVA Combination Therapy

In vitro data provided evidence that a combination of LUM and IVA might optimize CFTR-mediated chloride secretion in patients with CF carrying the *F508del-CFTR* mutation (see Section 3). Therefore, Phase 2 Study 102 was designed to evaluate LUM/IVA combination therapy. Patients homozygous for *F508del* were treated with LUM/IVA combination therapy for 28 days after completing the LUM monotherapy dosing period (Figure 19). Day 56 results represent the net effect of 28 days of LUM/IVA combination preceded by 28 days of LUM monotherapy, compared to the overall study baseline at Day 1.

Results from Cohort 1 of Study 102 led to the use of an increased IVA dosage (250 mg q12h) when administered in combination with LUM compared with the approved IVA dosage administered as monotherapy (150 mg q12h). This increase in IVA dosage was due to the reduction in IVA exposure due to cytochrome P450 (CYP) 3A induction by LUM (see Section 6). With the 250 mg q12h dosage, IVA exposures in the combination regimens were lower than those with IVA 150 mg q12h as monotherapy, but were expected to be adequate because IVA has a higher potency for F508del-CFTR than for G551D-CFTR (EC_{50} value of 2 nM versus 20 nM).

Study 102 demonstrated that treatment of patients homozygous for *F508del* with LUM/IVA combination therapy improved sweat chloride compared to placebo. The greatest change was seen with LUM400q12h/IVA (-11.0 mmol/L compared with placebo) (Table 11). At every dose level, the LUM/IVA combination therapy response is greater than that for LUM monotherapy, which is consistent with in vitro results (Section 3.5).

Improvements in $ppFEV_1$ were observed with LUM/IVA combination therapy. As shown in Table 11, the two regimens with the highest total daily dose of LUM (LUM600qd/IVA and LUM400q12h/IVA) showed consistent improvements in sweat chloride and the greatest improvements from baseline in absolute change in $ppFEV_1$. The results at the end of LUM/IVA combination therapy (Day 56) were also compared to results at the end of LUM monotherapy (Day 28); as expected, given the decline in $ppFEV_1$ with LUM monotherapy, the largest improvements in absolute change in $ppFEV_1$ were observed with LUM600qd/IVA (6.2 percentage points; data not shown) and LUM400q12h/IVA (6.1 percentage points; data not shown).

Table 11 Sweat Chloride and $ppFEV_1$ Assessments at Day 56 (End of LUM/IVA Combination Dosing), Study 102

Endpoint	LUM200qd/IVA N = 21	LUM400qd/IVA N = 20	LUM600qd/IVA N = 20	LUM400q12h/IVA N = 11
Sweat chloride: Change from baseline at Day 56				
Treatment difference versus placebo (95% CI)	-5.0 (-10.5, 0.5) *P* = 0.073	-9.8 (-15.3, -4.3) *P*<0.001	-9.5 (-15.1, -3.9) *P* = 0.001	-11.0 (-18.3, -3.7) *P* = 0.004
Absolute change in $ppFEV_1$: Change from baseline at Day 56				
Treatment difference versus placebo (95% CI)	3.8 (-0.5, 8.1) *P* = 0.082	2.7 (-1.7, 7.0) *P* = 0.228	5.6 (1.2, 10.0) *P* = 0.014	4.2 (-1.3, 9.7) *P* = 0.137

Study 102 also confirmed that LUM/IVA combination therapy did not provide clinically meaningful benefit in patients heterozygous for the *F508del-CFTR* mutation who had a second mutation on the other allele that was predicted to result in a lack of CFTR production or not to respond to IVA based on in vitro testing.

5.2 Clinical Safety

Overall, LUM monotherapy and LUM/IVA combination therapy was well tolerated in Study 102. The majority of adverse events (AEs) were mild or moderate in severity and were consistent with the expected manifestations of CF disease. The most common AEs during LUM monotherapy and LUM/IVA combination therapy observed in the active treatment groups and placebo groups were cough, infective pulmonary exacerbation of CF, headache, productive cough, upper respiratory tract infection, nausea, hemoptysis, respiration abnormal (verbatim term: respiratory chest tightness), and dyspnea. There were no consistent clinically important trends attributable to LUM/IVA combination in the clinical laboratory results.

The AEs of dyspnea and respiration abnormal appeared potentially associated with LUM, as they occurred more commonly in subjects who received higher doses of LUM monotherapy compared with LUM/IVA combination therapy or placebo. Spirometry was assessed following dosing with LUM/IVA to investigate this finding further: short-term declines in ppFEV1 were observed immediately postdose in healthy subjects 18 years of age and older (Study 009) and in pediatric CF patients 6 through 11 years of age (Study 011). These $ppFEV_1$ declines were only rarely associated with AEs, and $ppFEV_1$ levels returned to, or near, baseline within 7 days of continued dosing; the effect was ameliorated by treatment with long-acting bronchodilators and reversed by treatment with short-acting inhaled bronchodilators. Based on these data this effect was expected to be limited in duration and clinically manageable.

5.3 Treatment Regimens Evaluated in Phase 3 Studies

Results from Study 102 suggested that both LUM600qd/IVA and LUM400q12h/IVA were clinically effective and safe dose regimens. These regimens demonstrated the greatest improvements in ppFEV1 with consistent improvements in sweat chloride. While these 2 dosing regimens appeared to be very similar in Phase 2, the LUM400q12h/IVA regimen was included in the Phase 3 studies, given the simplicity of this dosing regimen and its potentially advantageous PK profile. The LUM400q12h/IVA regimen allows for an approximately 2-fold increase in the expected trough concentration relative to the LUM600qd/IVA regimen and reduced peak-to-trough ratio while incurring only a modest increase in the total daily dose and exposure of LUM.

The LUM600qd/IVA regimen was supplied as a combination of fixed-dose combination (FDC) tablets and IVA tablets; the LUM400q12h/IVA regimen was supplied as FDC tablets (Figure 33 on page 87).

The results of Study 770-104 were consistent with in vitro findings and the mechanistic understanding of the underlying defect in F508del-CFTR, which suggested that there is not enough F508del-CFTR protein on the cell surface for CFTR potentiation alone might not to lead to clinical benefit because . Based on the consistent cumulative evidence, it was concluded that IVA alone is not effective in patients homozygous for *F508del* (see Kalydeco

USPI). Therefore, an IVA monotherapy arm was not included in the LUM/IVA Phase 3 studies.

Results from Study 102 showed a dose-dependent decline ppFEV$_1$ during treatment with LUM monotherapy. Given these results, LUM monotherapy was considered unlikely to provide clinical benefit, and therefore a LUM monotherapy arm was not included in the Phase 3 studies.

6 CLINICAL PHARMACOLOGY

Summary

- Coadministration with a high-fat meal significantly increased the exposures of LUM and IVA by approximately 2.0 fold and 3.0-fold, respectively. Therefore, it is recommended that LUM/IVA combination therapy be taken with fat-containing food.
- No dose adjustments of LUM/IVA are necessary based on weight, age, or sex.
- No dose adjustment is recommended for patients with CF who have mild hepatic impairment (Child-Pugh A). A 25% dose reduction is recommended for patients with moderate hepatic impairment (Child-Pugh B). LUM/IVA combination therapy has not been studied in patients with severe hepatic impairment (Child-Pugh C); however, exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, it is recommended to use LUM/IVA with caution in patients with severe hepatic impairment, and only if the benefits are expected to outweigh the risks.
- No dose adjustment is recommended for patients with mild or moderate renal impairment. Caution is recommended when administering LUM/IVA combination therapy to patients with severe renal impairment or with end-stage renal disease.
- LUM is a strong inducer of CYP3A. The net effect of LUM/IVA therapy is expected to be strong CYP3A induction. Coadministration of LUM/IVA is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index.
- Concomitant use of strong CYP3A inhibitors is not expected to impact LUM exposure, but is expected to increase IVA exposure. No dose adjustment is necessary when CYP3A inhibitors are initiated in patients taking LUM/IVA.
- Concomitant use of strong CYP3A inducers is not expected to impact LUM exposure, but is expected to decrease IVA exposure. Therefore, coadministration of LUM/IVA combination therapy is not recommended with strong CYP3A inducers.
- LUM/IVA does not prolong the QTc interval.
- A trend of greater reduction in sweat chloride with increasing exposure of LUM was observed for LUM doses ranging from 25 mg qd to 400 mg q12h. For LUM/IVA combinations that were evaluated, a trend for additional reduction in sweat chloride was observed with addition of IVA.

6.1 Pharmacokinetic Profiles of LUM and IVA

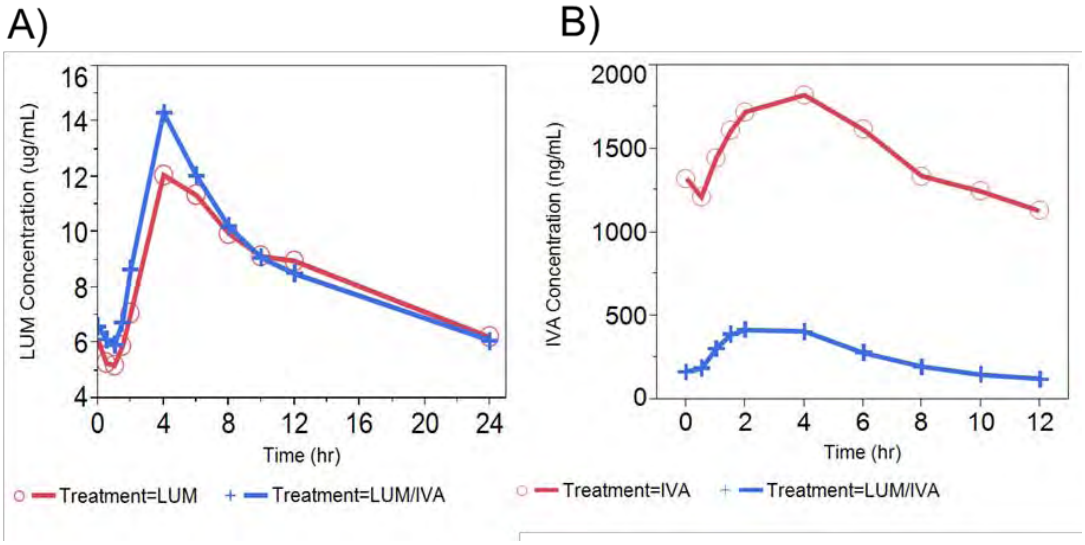
The PK profile of LUM was investigated in healthy subjects, CF patients, and special populations (subjects with hepatic impairment). In patients with CF, LUM C_{max} and AUC increased approximately proportionally with dose, over a range of doses from LUM 25 mg qd to 400 mg q12h. The mean plasma LUM terminal phase half-life ($t_{1/2}$) was approximately 26 hours. After twice daily dosing, steady state plasma concentrations of LUM in healthy subjects were generally reached after approximately 7 days of treatment, with an accumulation ratio of approximately 1.9. The PK variability of LUM was moderate across studies (%CV of approximately 30 to 40% for AUC).

The PK profile of IVA was previously characterized in the IVA monotherapy program. The highest doses investigated in the IVA monotherapy program was 450 mg q12h for 5 days in healthy subjects and 250 mg q12h in CF patients. IVA exposure is similar between healthy adult subjects and patients with CF. PK characteristics of IVA when given in combination with LUM were further investigated for the LUM development program in healthy subjects and CF patients. After q12h dosing in combination with LUM, steady state plasma concentrations of IVA in healthy subjects were generally reached after approximately 7 days of treatment. Due to the delayed onset of the induction effect of LUM (Section 6.1.1), IVA exposures are highest on the first few days of treatment with steady-state exposure being lower than that of Day 1. In healthy subjects, the $t_{1/2}$ of IVA when given in combination with LUM is approximately 9 hours. The PK variability of IVA given in combination with LUM was moderate to high across studies (%CV of approximately 60% for AUC).

6.1.1 Interaction Between LUM and IVA

LUM is a strong inducer of CYP3A. Co-administration of LUM with IVA, a sensitive CYP3A substrate, substantially decreased IVA exposure by 80% (Study 005, Figure 18B); however, IVA has minimal impact on the exposures of LUM in healthy subjects (Study 005, Figure 20A). Therefore, the IVA dosage in the LUM combination therapy regimen is higher (250 mg q12h) than the approved IVA monotherapy dosage (150 mg q12h). The net exposure of IVA given as 250 mg q12h in the combination therapy is approximately one-third that when given as monotherapy. Because IVA has higher in vitro potency for F508del-CFTR than for G551D−CFTR expressing cells (EC_{50} values of 2 nM versus 20 nM), the reduced IVA exposure is expected to be sufficient for patients homozygous for *F508del*.

Figure 20 Steady-State Plasma Concentration Profiles of LUM and IVA When LUM and IVA Were Administered Alone or in Combination



6.1.2 LUM/IVA Exposure in Phase 3 Studies

For comparison of exposures between doses included in the Phase 3 studies, Table 12 summarizes observed concentration values and model-predicted AUC values, which were both pooled across Studies 103 and 104. The LUM400q12h/IVA regimen has a 33% higher total daily dose, and thus the difference in exposure was modest, with extensive overlaps in exposures for both LUM and IVA. The key differentiation between the two regimens is the approximately 2-fold higher LUM trough concentration and lower peak-to-trough ratio for the q12h regimen.

Table 12 Summary of Pooled PK Parameters from Studies 103 and 104

	LUM600qd/IVA[a]			LUM400q12h/IVA[a]			Ratio of Analytes LUM600qd/IVA to LUM400q12h/IVA[b]		
Analyte	$C_{0h,ave}$ (µg/mL)	$C_{3\text{-}6h,ave}$ (µg/mL)	AUC[c] [µg·h/mL]	$C_{0h,ave}$ (µg/mL)	$C_{3\text{-}6h,ave}$ (µg/mL)	AUC[c] [µg·h/mL]	$C_{0h,ave}$	$C_{3\text{-}6h,ave}$	AUC
LUM	6.81	28.0	336	12.4	23.3	432	1.82	0.83	1.29
IVA	0.112	0.580	4.02	0.0821	0.439	3.38	0.73	0.76	0.84

[a] Median values are reported.
[b] Ratios are based on reported median values.
[c] Estimated AUC values are based on population PK models; AUC is $AUC_{0\text{-}24h}$ for lumacaftor and $AUC_{0\text{-}12h}$ for IVA.

6.2 Absorption, Distribution, Metabolism, and Excretion

Following multiple oral doses of LUM, the exposure of LUM generally increased proportional to dose over the range of 50 mg to 1000 mg every 24 hours. The median (range) time of the maximum concentration (t_{max}) of LUM is approximately 4.0 hours (2.0; 9.0) in the fed state. Administration of FDC tablets with a high-fat meal increased the exposure of LUM by approximately 2.0-fold. LUM is approximately 99% bound to plasma proteins, primarily to albumin. LUM is not extensively metabolized in humans, with the majority of LUM excreted unchanged in the feces. There was negligible urinary excretion of LUM as unchanged parent. In vitro data indicate that CYP3A and glucuronidation are involved in the metabolism of LUM; however, based on clinical drug-drug interaction (DDI) studies demonstrating minimal impact on LUM exposures with strong inhibitor and inducer of CYP3A, CYP elimination pathway is likely to play a minimal role in the overall elimination of LUM.

Following multiple oral dose administration of IVA in combination with LUM, the exposure of IVA generally increased with doses from 150 mg q12h to 250 mg q12h. The median (range) t_{max} of IVA is approximately 4.0 hours (2.0; 6.0) in the fed state. Administration of FDC tablets with a high-fat meal increased the exposure of IVA by approximately 3.0-fold. LUM and IVA combination is recommended to be taken with fat-containing food. The human plasma protein binding of IVA was greater than 99%, primarily to alpha-1-acid glycoprotein and albumin. IVA is extensively metabolized in humans. In vitro and in vivo data indicate that IVA is primarily metabolized by CYP3A. M1-IVA and M6-IVA are the major metabolites of IVA in humans. M1-IVA has approximately one-sixth the activity of parent in vitro, and is considered pharmacologically active; M6-IVA has approximately $1/50^{th}$ the activity of parent in vitro, and is considered pharmacologically inactive. For IVA and its metabolites, elimination in the feces as metabolites was the predominant route of elimination, with negligible renal excretion of parent.

6.3 Effect of Intrinsic Factors on Pharmacokinetics

6.3.1 Demographic and Baseline Disease Characteristics

A pooled population PK analysis was conducted using data from Phase 1 (Studies 005, 006, and 011), Phase 2 (Studies 101 and 102), and Phase 3 studies (Studies 103 and 104). The effects of weight, age, sex, and disease state on LUM and IVA PK were assessed. Results from the analyses indicate that the demographic factors of weight, age, sex, do not have clinically meaningful effects on the PK of LUM and IVA, and no dose adjustment is warranted for these factors.

When evaluating the effect of disease status (CF patients versus non-CF patients) on PK, the LUM bioavailability was 1.81-fold higher in healthy subjects than in CF patients. There were also differences in other absorption parameters (i.e., rate of absorption, absorption lag). Disease state was not a significant covariate in previous population models of IVA monotherapy; however, when given in combination with LUM, the IVA bioavailability was 1.53-fold higher in healthy subjects.

6.3.2 Hepatic Impairment

Study with LUM/IVA combination therapy in subjects with moderate hepatic impairment (Child-Pugh B) showed higher exposures of LUM and IVA (AUC during a dosing interval [AUCτ] by approximately 50% and Cmax by approximately 30% for both components) in subjects with moderate hepatic impairment than in healthy subjects. Based on these results, no dose adjustment for LUM/IVA combination therapy is recommended for patients with CF who have mild hepatic impairment (Child-Pugh A), and a 25% dose reduction is recommended for patients with moderate hepatic impairment (Child-Pugh B).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh C); however, the impact on exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use in patients with severe hepatic impairment is recommended only if the benefits are expected to outweigh the risks; these patients should be closely monitored and the dose should be reduced at least 50% with a maximum dose of LUM 200 mg q12h/IVA 125 mg q12h.

6.3.3 Renal Impairment

LUM and IVA have not been studied in subjects with renal impairment. Human ADME studies with LUM and IVA showed negligible urinary excretion and that renal clearance is likely to have minimal role in the elimination of LUM and IVA. Based on these results, no dose adjustment is necessary for patients with mild to moderate renal impairment. Patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease may have reduced metabolic capacities. Therefore, caution is recommended when administering LUM/IVA combination therapy to patients with severe renal impairment or with end-stage renal disease.

6.4 Effect of Extrinsic Factors on Pharmacokinetics

6.4.1 Drug-Drug Interactions

6.4.1.1 Potential for LUM/IVA to Affect Other Drugs

Co-administration of LUM with IVA, a sensitive CYP3A substrate, substantially decreased IVA exposure by 80%, indicating that LUM is a strong inducer of CYP3A. IVA was previously shown to be a weak inhibitor of CYP3A when given as monotherapy. The net effect of LUM/IVA therapy is expected to be strong CYP3A induction.

In addition, in vitro studies suggest that LUM has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; however, inhibition of CYP2C8 and CYP2C9 by LUM has also been observed in vitro. In vitro studies suggest that IVA has the potential to inhibit both CYP2C8 and CYP2C9; however, IVA did not inhibit CYP2C8 in vivo. Therefore, concomitant use of LUM/IVA and CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates.

Based on in vitro results that show P-glycoprotein (P-gp) inhibition and pregnane-X-receptor activation, LUM has the potential to both inhibit and induce P-gp. A clinical study with IVA monotherapy showed that IVA is a weak inhibitor of P-gp. Therefore, coadministration of LUM/IVA combination therapy may alter the exposure of P-gp substrates.

Although LUM is a strong inducer of CYP3A, minimal clinically relevant drug interactions are expected with the major classes of common CF drugs such as allergy medications, bronchodilators, key CF antibiotics (e.g., azithromycin, ciprofloxacin, tobramycin), inhaled steroids, mucolytics and pancreatic enzymes. Notable interactions are expected with selected antifungals, GI drugs and anti-inflammatory drugs. In some instances, a higher dose of the concomitant drug may be used to address the interaction. Guidance for the management of observed and anticipated DDIs will be provided in the proposed labeling.

The effects of LUM monotherapy or LUM/IVA combination therapy on the PK of hormonal contraceptives have not been studied; however, since LUM is a strong inducer of CYP3A, it may reduce the effectiveness of hormonal contraceptives. Hormonal contraceptives should not be relied on as an effective method of contraception when coadministered with LUM/IVA combination therapy.

6.4.1.2 Potential for Other Drugs to Affect LUM/IVA

LUM is unlikely to be metabolized by CYP3A to any relevant extent in vivo, based on the CYP3A inhibitor and inducer DDI study. IVA was metabolized in vitro by recombinant CYP3A4 and CYP3A5, and was shown clinically to be a sensitive substrate of CYP3A. Neither LUM nor IVA is a substrate for uptake transporters organic anion-transporting polypeptides (OATP) 1B1 and OATP1B3.

A DDI study (Study 009) was performed in healthy subjects to evaluate the effect of ciprofloxacin, which is used frequently in the patient population with CF; a strong CYP3A inhibitor (itraconazole); and a strong CYP3A inducer (rifampin) on the PK of LUM in combination with IVA (Table 13). LUM exposure is not affected by concomitant administration of CYP3A inducers or inhibitors. Exposure of IVA when given in combination with LUM is reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors. Therefore, the potential for other drugs to affect LUM and IVA combination therapy is likely due to CYP3A inhibitors and inducers affecting the exposures of IVA.

Table 13 Impact of Other Drugs on LUM/IVA Exposures

Coadministered Drug	Dose of Coadministered Drug	Dose of LUM/IVA	Effect on PK[a]	Mean Ratio (90% CI) of LUM and IVA No Effect = 1.0	
				AUC	C_{max}
Ciprofloxacin	750 mg q12h	200 mg q12h LUM 250 mg q12h IVA	↔ LUM	0.86 (0.79, 0.95)	0.88 (0.80, 0.97)
			↔ IVA	1.29 (1.12, 1.48)	1.29 (1.11, 1.49)
Itraconazole	200 mg daily	200 mg q12h LUM 250 mg q12h IVA	↔ LUM	0.97 (0.91, 1.02)	0.99 (0.92, 1.05)
			↑ IVA[b]	4.30 (3.78, 4.88)	3.64 (3.19, 4.17)
Rifampin	600 mg daily	200 mg q12h LUM 250 mg q12h IVA	↔ LUM	0.87 (0.81, 0.93)	0.96 (0.87, 1.05)
			↓ IVA	0.43 (0.38, 0.49)	0.50 (0.43, 0.58)

[a] The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change)
[b] Due to the induction effect of LUM on CYP3A, at steady-state, the net exposure of IVA is not expected to exceed that when given in the absence of LUM at a dose of 150 mg q12h, the approved dose of IVA monotherapy.

Due to the induction effect of LUM on CYP3A, at steady-state, the net exposure of IVA when co-administered with a strong inhibitor is not expected to exceed that when given in the absence of LUM at a dose of 150 mg q12h, the approved dose of IVA monotherapy. Thus, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking LUM/IVA combination therapy. However, when initiating LUM/IVA combination therapy while taking a strong CYP3A inhibitor, an initial dose adjustment to 1 tablet (LUM200/IVA125) qd should be used for the first week of treatment to allow for the steady state induction effect of LUM. Co-administration of LUM/IVA is not recommended with strong CYP3A inducers.

6.5 Effect of LUM and IVA on QT Interval

The effect of multiple doses of LUM600qd/IVA250q12h and LUM1000qd/IVA450q12h on QTc interval was evaluated in a randomized, placebo- and active-controlled (400 mg of moxifloxacin), parallel, thorough QT study in 168 healthy subjects. No meaningful changes in QTc interval were observed with either LUM600qd/IVA 250 mg or LUM1000qd/ IVA450q12h dose groups. No statistically significant relationships between QTcF changes with LUM or IVA concentrations were determined from linear mixed-effects models.

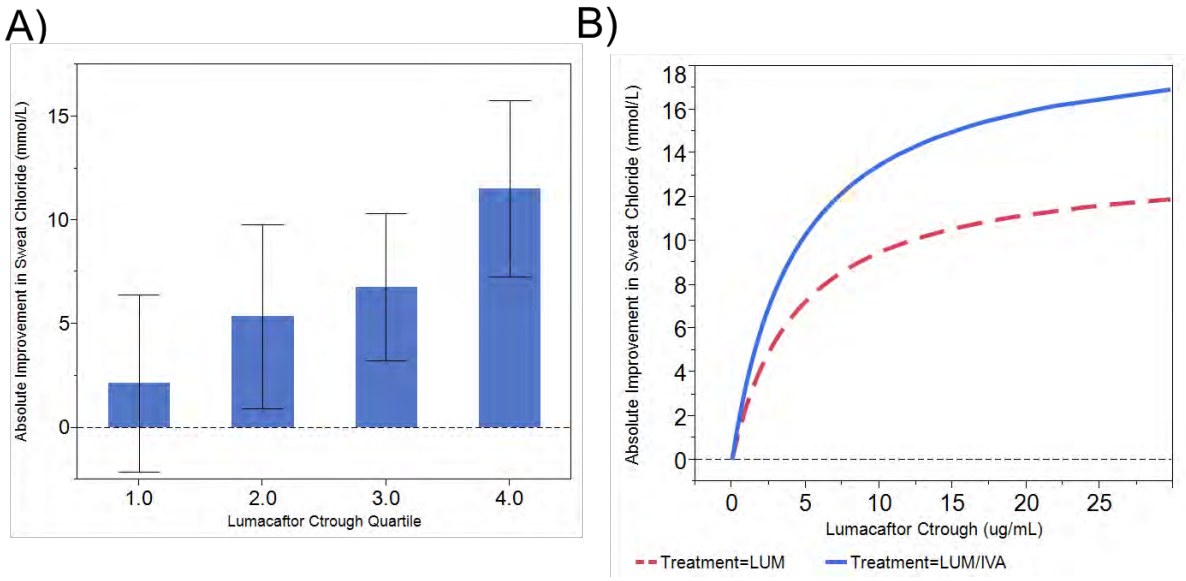
6.6 Exposure-Response for Sweat Chloride

Sweat chloride concentration is a direct measure of CFTR function and is used as a diagnostic indicator of CF and as a pharmacodynamic (PD) marker of on-target activity in CF clinical studies. In Phase 2 studies, a trend of greater reduction in sweat chloride with increasing exposure of LUM was observed for LUM doses ranging from 25 mg qd to 400 mg q12h. For LUM/IVA combinations that were evaluated (200 mg qd to 400 mg q12h), there

was a sweat chloride exposure response trend with respect to LUM concentrations (Figure 19A) and a trend for additional reduction in sweat chloride with addition of IVA. To characterize the pharmacologic effect of LUM and IVA on sweat chloride response, a population PK/PD model describing an exposure-response relationship for sweat chloride was developed based on the Phase 2 data. Sweat chloride responses following LUM monotherapy and combination therapy were well characterized using a direct E_{max} exposure-response model. The model projections of sweat chloride responses as a function of LUM concentrations with and without IVA are shown in Figure 21B.

To estimate the sweat chloride response for doses studied in Phase 3, the sweat chloride exposure-response model was used to predict individual sweat chloride responses based on observed individual plasma concentrations for patients in Phase 3. For LUM600qd/IVA250q12h, the mean (standard deviation [SD]) predicted sweat chloride response is 11.52 (2.62) mmol/L. For LUM400q12h/IVAq12h, the mean (SD) projected sweat chloride response is 13.96 (2.13) mmol/L. This model demonstrated a greater reduction in sweat chloride with increasing concentrations of LUM and enhancement of this effect with the addition of IVA.

Figure 21 Sweat Chloride Exposure-Response for LUM/IVA Combination Therapy in Phase 2



Note: Data in Panel A are from Study 102. Data in Panel B is simulated based on the sweat chloride exposure response model.
Panel A: Summary of mean observed sweat chloride changes from baseline by LUM trough concentration quartiles following treatment with LUM/IVA combination therapy for 28 days. Quartiles 1 and 4 represent patients with the lowest and highest LUM trough concentrations, respectively. For each subject, LUM trough concentrations and sweat chloride responses were pooled across the combination treatment period. Changes reflect an absolute improvement based on the reduction in sweat chloride. Each error bar is constructed using a 95% confidence interval of the mean.
Panel B: Characterization of sweat chloride exposure response using a direct E_{max} model. This model demonstrates a greater improvement in sweat chloride with increasing trough concentrations of LUM and an enhancement of this effect with the addition of IVA.

7 EFFICACY

Summary

In two Phase 3 studies in more than 1000 patients, LUM/IVA demonstrated rapid, sustained, and consistent efficacy over 24 weeks across all active treatment arms. Respiratory and systemic benefits include improved lung function, reduced pulmonary exacerbations (including severe exacerbations), and improved nutritional status, all of which were observed on top of patients' usual CF medications. Importantly, improvements in lung function and nutritional status were sustained through 48 weeks.

- Patient demographic and baseline characteristics were generally comparable in the placebo and LUM/IVA groups and were representative of the population of patients with CF for whom this combination therapy is intended.
- Both LUM/IVA regimens demonstrated rapid, clinically meaningful, and statistically significant improvements in lung function through 48 weeks, in contrast to the decline observed with the placebo group.
    - In Studies 103 and 104, analysis of the primary endpoint (absolute change from baseline in $ppFEV_1$) showed a consistent and highly statistically significant treatment effect for both dosing regimens in both studies that ranged from 2.6 to 4.0 percentage points ($P \leq 0.0004$).
    - Interim analysis results from the extension Study 105 showed that improvements in $ppFEV_1$ were sustained through 48 weeks of LUM/IVA combination therapy.
- There were substantial reductions in pulmonary exacerbations including those requiring hospitalizations or IV antibiotics. In the pooled analysis, a greater reduction in pulmonary exacerbations compared to placebo was observed in the LUM400q12h/IVA regimen (39%; rate ratio: 0.61) than the LUM600qd/IVA regimen (30%; rate ratio: 0.70).
- Meaningful improvements in BMI were observed through 48 weeks.
- Improvements in CFQ-R respiratory domain score favored both LUM/IVA regimens.
- Clinical improvements in lung function, pulmonary exacerbations, nutrition, and patient-reported outcomes were observed on top of the usual prescribed CF therapies.
- While both LUM/IVA regimens yielded similar improvements in lung function, BMI, and CFQ-R, the LUM400q12h/IVA regimen resulted in greater reductions in pulmonary exacerbations, including those requiring hospitalization and use of IV antibiotics.

7.1 Study Designs

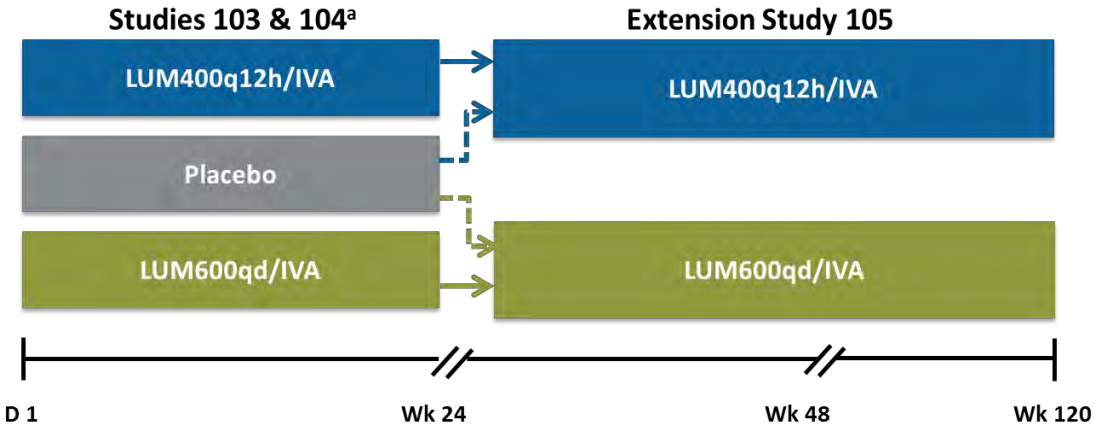
7.1.1 Studies 103 and 104

Studies 103 and 104 were Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of LUM/IVA combination therapy for 24 weeks in patients 12 years and older with CF who are homozygous for the *F508del-CFTR* mutation (Figure 22). The studies were identical except that Study 103 included assessment of ambulatory ECGs for a subset of US patients, and Study 104 included intensive PK sampling for a subset of US adolescent patients.

Eligible patients were randomized (1:1:1) to receive LUM600qd/IVA, LUM400q12h/IVA, or placebo. Randomization was stratified by age (<18 versus ≥18 years old), sex (male versus female), and screening ppFEV$_1$ (<70 versus ≥70). Patients took study drug in addition to their prescribed CF therapies.

Patients who prematurely discontinued study drug were to remain in the study through the Week 24 Visit.

Figure 22 Schematic of Study Design for Studies 103, 104, and 105



[a] Studies 103 and 104 were identical except that Study 103 included assessment of ambulatory ECGs for a subset of US patients, and Study 104 included intensive PK sampling for a subset of US adolescent patients

7.1.2 Study 105

Study 105 is an ongoing, Phase 3, parallel-group, multicenter, rollover study that is designed to evaluate the safety and efficacy of long-term LUM/IVA combination therapy (Figure 22). Patients treated with LUM/IVA in Study 103 or 104 continued to receive the same LUM/IVA dose regimen in a double-blind fashion. Patients who received placebo in Study 103 or 104 were randomized in a 1:1 ratio to LUM600qd/IVA and LUM400q12h/IVA; randomization was stratified by age in the previous study (<18 versus ≥18 years of age), sex, and ppFEV$_1$ at screening of the previous study (<70 versus ≥70).

An interim analysis of Study 105 was conducted after at least 100 patients had been exposed to LUM/IVA for 48 weeks (Study 103 or 104 plus Study 105) to provide additional safety data in support of the initial NDA. Efficacy analyses (ppFEV$_1$ and BMI) were also conducted as part of the interim analysis.

7.2 Study Population

Studies 103 and 104 enrolled patients ages 12 years and older who are homozygous for the *F508del-CFTR* mutation and had screening $ppFEV_1$ values between 40 and 90, inclusive. Several exclusion criteria were implemented to decrease potential confounders of study endpoint evaluations.

- The studies excluded patients whose CF disease may not have been stable (e.g., patients colonized with organisms associated with more rapid decline in pulmonary status, such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*; patients with recent acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease).
- Patients with a history of solid organ or hematological transplantation were excluded.
- Patients with screening safety laboratory results outside of specified limits were excluded.
- The studies prohibited use of strong inhibitors of CYP3A and moderate or strong inducers of CYP3A.

7.3 Endpoints

Statistical analysis plans for Studies 103 and 104 were developed and finalized before database lock and treatment unblinding per ICH guidelines, and took into account comments received from regulatory authorities. Table 14 shows the endpoints assessed in Studies 103 and 104. To minimize confounding effects on FEV_1, all spirometry assessments were to be performed after withholding bronchodilators.

Table 14 Endpoints in Studies 103 and 104

	Endpoint
Primary[a]	Absolute change from baseline in $ppFEV_1$ at Week 24[b]
Key Secondary[a]	Relative change from baseline in $ppFEV_1$ at Week 24[b]
	Absolute change from baseline in BMI at Week 24
	Absolute change from baseline in CFQ-R respiratory domain at Week 24
	Patients with ≥5% increase in relative change from baseline in $ppFEV_1$[b]
	Number of pulmonary exacerbations through Week 24[c]

Table 14 Endpoints in Studies 103 and 104

	Endpoint
Other Prespecified Endpoints	Absolute change in $ppFEV_1$ by visit
	Patients with ≥10% relative change from baseline in $ppFEV_1$[b]
	Number of pulmonary exacerbations requiring hospitalization
	Number of pulmonary exacerbations requiring IV antibiotics
	Time-to-first pulmonary exacerbation
	Safety, as determined by AEs, clinical laboratory values, standard digital ECGs, ambulatory ECGs (Study 103 only), vital signs, and pulse oximetry
	PK parameters of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA

[a] The primary and key secondary endpoints are shown in the order of the testing hierarchy.
[b] Change in $ppFEV_1$ at Week 24 was assessed as the average of the treatment effects at Week 16 and at Week 24 to provide a more precise estimate of the treatment effect at the end of the treatment period, given the inherent variability in $ppFEV_1$.
[c] The definition of a pulmonary exacerbation was based on the modified Fuchs criteria[31] (Section 7.7.2).

7.4 Statistical Methods

A mixed-effects model for repeated measures (MMRM) was used as the primary analysis method to determine the treatment effects. The model, including absolute change from baseline in $ppFEV_1$ (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex (male versus female), age group at baseline (<18 versus ≥18 years old), and $ppFEV_1$ severity at Screening (<70 versus ≥70), and patient as a random effect, was used to test the difference between each active combination treatment group versus the placebo group. The primary result obtained from the model was the average treatment effect at Week 16 and at Week 24. This analysis of the primary endpoint was performed to provide a more precise estimate of the treatment effect at the end of the treatment period given the inherent variability in $ppFEV_1$.

To ensure adequate control of the overall Type I error rate at 0.05 within each pivotal study in the presence of multiple endpoints across 2 dosing regimens, the following multiplicity adjustment approach was used and prespecified in the statistical analysis plans for Studies 103 and 104. A simple Bonferroni correction was first applied to adjust for multiplicity across 2 active doses. Then, a hierarchical testing procedure was used for the primary and key secondary endpoints at $\alpha = 0.0250$ for each active dose to adjust for multiplicity across multiple endpoints. At each step, the test for treatment effect was considered statistically significant if the *P* value was ≤0.0250, and all previous tests also met this level of significance. Table 14 shows the primary and key secondary endpoints in the order of the testing hierarchy.

If the hierarchy was broken, nominal *P* values were provided. For key secondary endpoints, treatment effects that were not considered statistically significant within the framework of the testing hierarchy were considered nominally significant if the *P* value was ≤0.0250. Other prespecified endpoints were tested at $\alpha = 0.0250$ level for each dose.

Data from Studies 103 and 104 were pooled for analysis because of the similarity in the study design, population, and treatment regimens. Analysis of pooled data facilitated exploration of any possible trends in subpopulations and provided more precise estimates of treatment effects for endpoints with fewer events, including reductions in pulmonary exacerbations. The consistency of results across both studies further supported evaluating efficacy based on pooled data. The hierarchical testing procedure was not used for the pooled analyses; treatment effects were considered statistically significant if the *P* value was ≤0.0250.

An interim analysis was performed when at least 100 patients had been exposed to LUM/IVA for approximately 48 weeks (in Study 103 or 104 plus Study 105) and included all available data up to the date of the database snapshot. (Therefore, the sample size varied across time points.) Analysis of efficacy was performed for up to 48 total weeks of treatment with LUM/IVA. All efficacy analyses were performed using data from the period beginning with the first dose of study drug in Studies 103 and 104 to the last dose of study drug in Study 105, excluding the period between 29 days after the last dose of Studies 103 and 104 and the first dose of Study 105.

7.5 Patient Disposition

Disposition data were similar for the 2 studies and between the LUM600qd/IVA and LUM400q12h/IVA groups (Table 15). A high proportion of patients completed treatment (95.1%) and enrolled in extension Study 105 (93.1%).

A higher percentage of patients discontinued treatment in the LUM/IVA groups than in the placebo group (5.4% in the LUM600qd/IVA group, 6.8% in the LUM400q12h/IVA group, and 2.4% in the placebo group). Treatment discontinuation rates were generally similar in the LUM600qd/IVA and LUM400q12h/IVA groups.

The most frequent reason for discontinuation from study drug treatment across groups was an AE. A higher percentage of subjects discontinued treatment due to an AE in the LUM/IVA groups than the placebo group (3.8% in LUM600qd/IVA group, 4.6% in LUM400q12h/IVA group, and 1.6% in placebo group). Discontinuation rates due to an AE were similar in the LUM600qd/IVA and the LUM400q12h/IVA groups.

Table 15 Patient Disposition, Studies 103 and 104

Disposition Reason	Study 103				Study 104				Pooled Studies 103 and 104			
	Placebo N=184 n (%)	LUM 600qd/ IVA N=183 n (%)	LUM 400q12h/ IVA N=182 n (%)	Overall N=549 n (%)	Placebo N=187 n (%)	LUM 600qd/ IVA N=185 n (%)	LUM 400q12h/ IVA N=187 n (%)	Overall N=559 n (%)	Placebo N=371 n (%)	LUM 600qd/ IVA N=368 n (%)	LUM 400q12h/ IVA N=369 n (%)	Overall N=1108 n (%)
Randomized	187	185	187	559	187	187	189	563	374	372	376	1122
Withdrew before study drug dosing	3	2	5	10	0	2	2	4	3	4	7	14
Received study drug	184	183	182	549	187	185	187	559	371	368	369	1108
Completed Treatment	180 (97.8)	172 (94.0)	172 (94.5)	524 (95.4)	182 (97.3)	176 (95.1)	172 (92.0)	530 (94.8)	362 (97.6)	348 (94.6)	344 (93.2)	1054 (95.1)
Discontinued Treatment	4 (2.2)	11 (6.0)	10 (5.5)	25 (4.6)	5 (2.7)	9 (4.9)	15 (8.0)	29 (5.2)	9 (2.4)	20 (5.4)	25 (6.8)	54 (4.9)
AE	4 (2.2)	8 (4.4)	6 (3.3)	18 (3.3)	2 (1.1)	6 (3.2)	11 (5.9)	19 (3.4)	6 (1.6)	14 (3.8)	17 (4.6)	37 (3.3)
Patient refused further dosing	0	2 (1.1)	1 (0.5)	3 (0.5)	2 (1.1)	1 (0.5)	1 (0.5)	4 (0.7)	2 (0.5)	3 (0.8)	2 (0.5)	7 (0.6)
Did not meet eligibility criteria	0	0	2 (1.1)	2 (0.4)	0	0	0	0	0	0	2 (0.5)	2 (0.2)
Noncompliance with study drug	0	0	0	0	0	0	2 (1.1)	2 (0.4)	0	0	2 (0.5)	2 (0.2)
Physician decision	0	0	1 (0.5)	1 (0.2)	0	0	0	0	0	0	1 (0.3)	1 (0.1)
Requires prohibited medication	0	0	0	0	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)	1 (0.3)	1 (0.3)	0	2 (0.2)
Pregnancy (self or partner)	0	1 (0.5)	0	1 (0.2)	0	0	0	0	0	1 (0.3)	0	1 (0.1)
Other[a]	0	0	0	0	0	1 (0.5)	1 (0.5)	2 (0.4)	0	1 (0.3)	1 (0.3)	2 (0.2)

Notes: Percentages were calculated relative to the number of patients in the FAS, which was defined as all randomized patients who received any amount of study drug.

[a] Other reasons for discontinuing treatment were missing the Week 16 Visit and out-of-window for the Week 24 Visit and ineligible genotype.

7.6 Demographic and Baseline Characteristics

Key patient demographic and baseline characteristics are summarized in Table 16. Demographic and baseline characteristics were generally balanced between the 3 treatment groups within each study and across the 2 studies. In the pooled Study 103 and 104 dataset, about 50% of the patients were female, the mean (SD) age was 25.0 (9.68) years, the mean (SD) BMI was 21.18 (3.006) kg/m^2, and the mean (SD) $ppFEV_1$ at baseline was 60.6 (13.81) (range: 31.1, 99.8).

Table 16 Patient Demography and Baseline Disease Characteristics, Studies 103 and 104, FAS

	Study 103				Study 104				Pooled Studies 103 and 104			
Variable	Pbo N = 184	LUM 600qd/ IVA N = 183	LUM 400q12h/ IVA N = 182	Overall N = 549	Pbo N = 187	LUM 600qd/ IVA N = 185	LUM 400q12h/ IVA N = 187	Overall N = 559	Pbo N = 371	LUM 600qd/ IVA N = 368	LUM 400q12h/ IVA N = 369	Overall N = 1108
Sex, n (%)												
Female	84 (45.7)	86 (47.0)	84 (46.2)	254 (46.3)	97 (51.9)	96 (51.9)	98 (52.4)	291 (52.1)	181 (48.8)	182 (49.5)	182 (49.3)	545 (49.2)
Age (years)												
Mean	25.0	24.7	25.5	25.1	25.7	24.3	25.0	25.0	25.4	24.5	25.3	25.0
SD	10.80	9.71	10.09	10.20	10.02	8.31	9.03	9.16	10.41	9.03	9.56	9.68
Median	22.0	23.0	23.5	23.0	24.0	23.0	24.0	24.0	23.0	23.0	24.0	23.0
Min, max	12, 64	12, 54	12, 57	12, 64	12, 55	12, 48	12, 54	12, 55	12, 64	12, 54	12, 57	12, 64
Age group, n (%)												
12 to <18 years	53 (28.8)	53 (29.0)	52 (28.6)	158 (28.8)	43 (23.0)	43 (23.2)	46 (24.6)	132 (23.6)	96 (25.9)	96 (26.1)	98 (26.6)	290 (26.2)
≥18 years	131 (71.2)	130 (71.0)	130 (71.4)	391 (71.2)	144 (77.0)	142 (76.8)	141 (75.4)	427 (76.4)	275 (74.1)	272 (73.9)	271 (73.4)	818 (73.8)
$ppFEV_1$												
Mean	60.5	61.2	60.5	60.7	60.4	60.5	60.6	60.5	60.4	60.8	60.5	60.6
SD	13.22	13.31	14.29	13.59	14.32	13.83	14.01	14.03	13.77	13.56	14.13	13.81
Median	60.4	61.8	58.7	60.4	60.5	60.6	61.5	60.9	60.5	61.0	60.4	60.6
Min, max	34.0, 88.0	31.1, 92.3	34.8, 94.0	31.1, 94.0	33.9, 99.8	34.4, 90.4	31.3, 96.5	31.3, 99.8	33.9, 99.8	31.1, 92.3	31.3, 96.5	31.1, 99.8
$ppFEV_1$, n (%)												
<40[a]	11 (6.0)	12 (6.6)	12 (6.6)	35 (6.4)	17 (9.1)	12 (6.5)	17 (9.1)	46 (8.2)	28 (7.5)	24 (6.5)	29 (7.9)	81 (7.3)
≥40 to <70	122 (66.3)	122 (66.7)	116 (63.7)	360 (65.6)	116 (62.0)	119 (64.3)	117 (62.6)	352 (63.0)	238 (64.2)	241 (65.5)	233 (63.1)	712 (64.3)
≥70 to ≤90	48 (26.1)	47 (25.7)	51 (28.0)	146 (26.6)	49 (26.2)	51 (27.6)	49 (26.2)	149 (26.7)	97 (26.1)	98 (26.6)	100 (27.1)	295 (26.6)
>90	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)	3 (1.6)	2 (1.1)	2 (1.1)	7 (1.3)	3 (0.8)	3 (0.8)	3 (0.8)	9 (0.8)
BMI (kg/m^2)												
Mean	21.03	21.06	21.68	21.25	21.02	20.97	21.32	21.10	21.02	21.02	21.50	21.18
SD	2.956	2.815	3.169	2.993	2.887	3.269	2.894	3.019	2.918	3.048	3.034	3.006
Median	20.80	21.00	21.20	20.90	20.90	20.70	21.10	21.00	20.90	20.80	21.10	20.90
Min, max	14.4, 32.2	14.3, 28.7	14.6, 29.8	14.3, 32.2	14.1, 29.7	14.2, 35.1	14.8, 31.4	14.1, 35.1	14.1, 32.2	14.2, 35.1	14.6, 31.4	14.1, 35.1

Baseline values are shown. Baseline was defined as the most recent measurement before the first dose of study drug.

[a] Patients with $ppFEV_1$ <40 at screening were excluded. However, 81 patients (35 patients in Study 103 and 46 patients in Study 104) had $ppFEV_1$ <40 at baseline (range: 31.1 to 39.9). The majority of these patients (96.3%) completed treatment.

The study population was treated with common CF therapies (bronchodilators, dornase alfa, inhaled antibiotics, azithromycin, inhaled hypertonic saline, and inhaled corticosteroids) (Table 17; data shown are percentage of patients that used the medication). During the studies, patients continued to receive their prescribed therapies for CF, and use of these concomitant medications remained generally stable throughout the treatment period.

Table 17 Prior Use of CF Therapies by Study Population, Pooled Studies 103 and 104 FAS

CF Therapy	Placebo N = 371 %	LUM600qd/IVA N = 368 %	LUM400q12h/IVA N = 369 %	Overall N = 1108 %
Bronchodilators (any)	92.2	92.9	93.2	92.8
Dornase alfa	75.7	78.5	74.0	76.1
Inhaled antibiotics	69.5	63.0	61.0	64.5
Azithromycin	62.8	63.3	58.3	61.5
Inhaled hypertonic saline	59.3	53.5	61.5	58.1
Inhaled corticosteroids	59.3	57.9	57.5	58.2

7.7 Efficacy Results

Analyses of the primary and key secondary endpoints are shown in Table 18.

The primary endpoint was met with high statistical significance in Studies 103 and 104 as well as the pooled analysis ($P \leq 0.0004$) for all active treatment arms.

Outcomes favored treatment with LUM/IVA over placebo for all key secondary endpoints: relative change in $ppFEV_1$, change in BMI, change in CFQ-R respiratory domain score, patients with ≥5% relative improvement in $ppFEV_1$, and number of pulmonary exacerbations (Table 18). Relative $ppFEV_1$ was statistically significant in both studies, and BMI was statistically significant in Study 104. The testing hierarchy was broken at BMI in Study 103 and CFQ-R respiratory domain in Study 104. All comparisons, whether statistically significant, nominally significant ($P \leq 0.0250$, but not considered statistically significant within the framework of the testing hierarchy), or not significant, favored LUM/IVA.

Several endpoints were nominally significant ($P \leq 0.0250$, but not considered statistically significant within the framework of the testing hierarchy): CFQ-R respiratory domain for LUM600qd/IVA group in Study 103, patients with ≥5% relative improvement in $ppFEV_1$ for both LUM/IVA groups in both studies, and number of pulmonary exacerbation rate for the LUM400q12h/IVA group in Study 103 and both LUM/IVA groups in Study 104.

In the pooled analysis of Studies 103 and 104, both LUM/IVA regimens resulted in statistically significant improvements in relative change in $ppFEV_1$, patients with relative improvements in $ppFEV_1$ ≥5%, number of pulmonary exacerbations, and change in BMI ($P \leq 0.0250$).

Table 18 Studies 103 and 104: Primary and Key Secondary Endpoints, FAS

Endpoint Comparison	Study 103		Study 104		Pooled Studies 103 and 104	
	LUM600qd/ IVA N = 183	LUM400q12h/ IVA N = 182	LUM600qd/ IVA N = 185	LUM400q12h/ IVA N = 187	LUM600qd/ IVA N = 368	LUM400q12h / IVA N = 369
Primary: Absolute change from baseline in $ppFEV_1$						
Treatment difference to placebo (95% CI)	4.0 (2.6, 5.4) *P*<0.0001	2.6 (1.2, 4.0) *P* = 0.0003	2.6 (1.2, 4.1) *P* = 0.0004	3.0 (1.6, 4.4) *P*<0.0001	3.3 (2.3, 4.3) *P*<0.0001	2.8 (1.8, 3.8) *P*<0.0001
Key Secondary: Relative change from baseline in $ppFEV_1$						
Treatment difference to placebo (95% CI)	6.7 (4.3, 9.2) *P*<0.0001	4.3 (1.9, 6.8) *P* = 0.0006	4.4 (1.9, 7.0) *P* = 0.0007	5.3 (2.7, 7.8) *P*<0.0001	5.6 (3.8, 7.3) *P*<0.0001	4.8 (3.0, 6.6) *P*<0.0001
Key Secondary: Change from baseline in BMI						
Treatment difference to placebo (95% CI)	0.16 (-0.04, 0.35) *P* = 0.1122	0.13 (-0.07, 0.32) *P* = 0.1938	0.41 (0.23, 0.59) *P*<0.0001	0.36 (0.17, 0.54) *P* = 0.0001	0.28 (0.15, 0.41) *P*<0.0001	0.24 (0.11, 0.37) *P* = 0.0004
Key Secondary: Change from baseline in CFQ-R respiratory domain						
Treatment difference to placebo (95% CI)	3.9 (0.7, 7.1) *P* = 0.0168[a]	1.5 (-1.7, 4.7) *P* = 0.3569	2.2 (-0.9, 5.3) *P* = 0.1651	2.9 (-0.3, 6.0) *P* = 0.0736	3.1 (0.8, 5.3) *P* = 0.0071	2.2 (0.0, 4.5) *P* = 0.0512
Key Secondary: Patients with ≥5% relative improvement in $ppFEV_1$						
Odds ratio to placebo (95% CI)	2.94 (1.88, 4.59) *P*<0.0001[a]	2.06 (1.29, 3.28) *P* = 0.0023[a]	2.96 (1.88, 4.64) *P*<0.0001[a]	2.38 (1.52, 3.73) *P* = 0.0001[a]	2.95 (2.15, 4.05) *P*<0.0001	2.22 (1.61, 3.07) *P*<0.0001
Key Secondary: Number of pulmonary exacerbations						
Rate ratio to placebo (95% CI)	0.72 (0.52, 1.00) *P* = 0.0491	0.66 (0.47, 0.93) *P* = 0.0169[a]	0.69 (0.52, 0.92) *P* = 0.0116[a]	0.57 (0.42, 0.76) *P* = 0.0002[a]	0.70 (0.56, 0.87) *P* = 0.0014	0.61 (0.49, 0.76) *P*<0.0001

Notes: Within each treatment group for Studies 103 and 104, the treatment difference was considered statistically significant if $P \leq 0.0250$, and if all previous tests within the testing hierarchy also met this level of significance. For the analysis of pooled data from Studies 103 and 104, a testing hierarchy was not applied, and the treatment difference was considered statistically significant if $P \leq 0.0250$.

[a] Endpoint was nominally significant at $P \leq 0.0250$ level; however, it was not considered statistically significant within the framework of the testing hierarchy.

7.7.1 Lung Function ($ppFEV_1$)

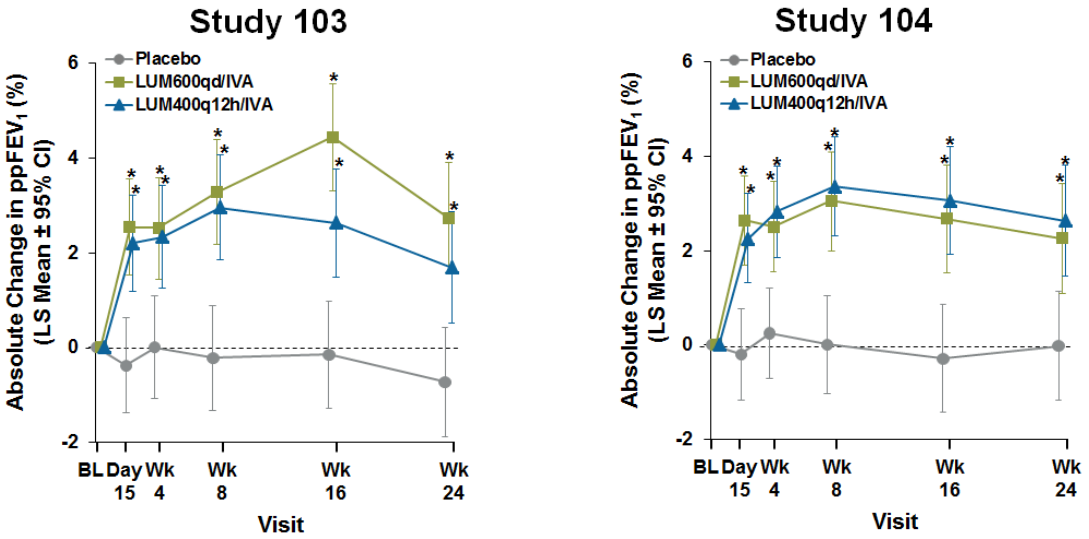
FEV_1 as measured by spirometry is the most widely implemented standardized assessment to evaluate lung function in CF. To normalize spirometry parameters across patients of varying age, height, and sex, percent predicted values were determined.[65,-,67]

In Studies 103 and 104, consistent and highly statistically significant improvements in $ppFEV_1$ that were rapid in onset (by Day 15) and sustained across all visits during the 24-week treatment period were observed in both LUM/IVA regimens.

Analysis of the primary endpoint (absolute change from baseline in $ppFEV_1$) showed a consistent and highly statistically significant treatment effect for both dosing regimens in both studies (Table 18). The absolute improvements in $ppFEV_1$ relative to placebo ranged from 2.6 to 4.0 percentage points across both studies and both LUM/IVA regimens ($P \leq 0.0004$).

Statistically significant improvements in $ppFEV_1$ were rapid in onset and were detected by Day 15 for both LUM/IVA regimens in both studies (Figure 23). Sustained improvements in $ppFEV_1$ were observed across all visits during the 24-week treatment period. In contrast, the absolute change in $ppFEV_1$ for the placebo groups remained stable or declined slightly over 24 weeks of treatment.

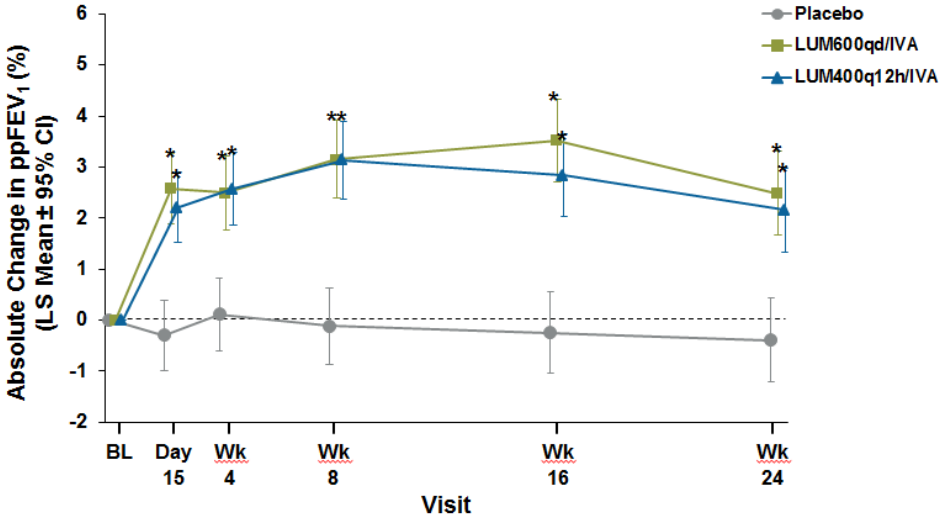
Figure 23 Absolute Change in $ppFEV_1$ Over Time, Studies 103 and 104, FAS



* indicates $P<0.0250$ compared to placebo

The pooled analysis of the primary endpoint also showed rapid, consistent, and sustained improvements in $ppFEV_1$ for both LUM/IVA regimens (Figure 24). The absolute improvement in $ppFEV_1$ relative to placebo was 3.3 percentage points for the LUM600qd/IVA regimen and 2.8 percentage points for the LUM400q12h/IVA regimen ($P<0.0001$ for both regimens). While the absolute improvements in $ppFEV_1$ were similar for the 2 LUM/IVA regimens, the pooled analysis numerically favored the LUM600qd/IVA regimen over the LUM400q12h/IVA regimen. This trend was not consistently observed in the individual studies; in Study 104, the LUM400q12h/IVA dosing regimen had a numerically higher improvement in $ppFEV_1$ (Table 18). Thus, there was no clear differentiation between the 2 combination therapy regimens when absolute change in $ppFEV_1$ was evaluated.

Figure 24 Absolute Change in ppFEV$_1$ Over Time, Pooled Studies 103 and 104, FAS

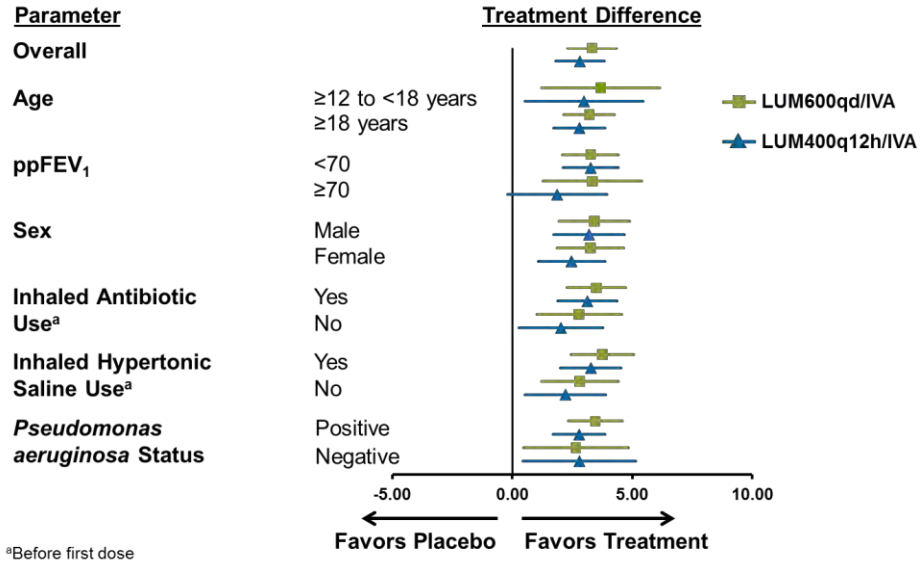


* indicates $P<0.0250$ compared to placebo

	Number of Patients					
	BL	Day 15	Wk 4	Wk 8	Wk 16	Wk 24
Placebo	366	351	353	346	353	350
LUM600qd/IVA	366	349	349	344	345	346
LUM400q12h/IVA	365	356	349	339	344	339

Subgroup analyses of the pooled Studies 103 and 104 datasets showed consistent efficacy regardless of age, sex, ppFEV$_1$ at screening, prior use of common CF medications, and *P. aeruginosa* infection (Figure 25). There were no significant treatment-by-interaction *P* values for these subgroups (*P* values ranged from 0.1183 to 0.9479).

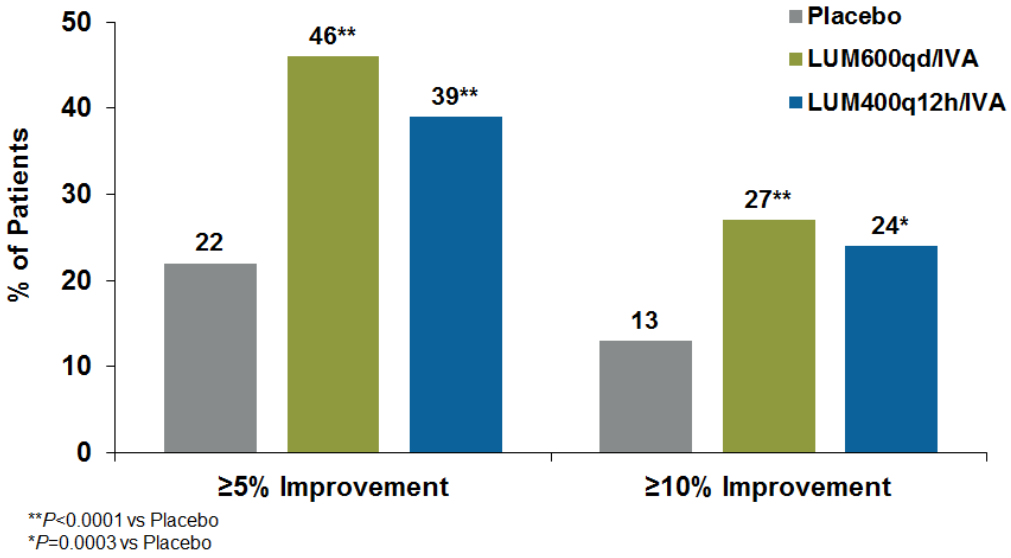
Figure 25 Subgroup Analyses of Absolute Change in ppFEV$_1$, Pooled Studies 103 and 104, FAS



Analysis of the first key secondary endpoint, relative change in $ppFEV_1$, yielded robust and significant improvements in both studies that ranged from 4.3% to 6.7% ($P \leq 0.0007$; Table 18). In the pooled analysis, the relative change in $ppFEV_1$ compared to placebo was 5.6% for the LUM600qd/IVA regimen and 4.8% for the LUM400q12h/IVA regimen ($P<0.0001$ for both regimens).

The proportion of patients with a ≥5% relative improvement in $ppFEV_1$ was a key secondary endpoint. In Studies 103 and 104, analysis of patients meeting this threshold change in $ppFEV_1$ favored both LUM/IVA regimens. The odds ratio to placebo ranged from 2.06 to 2.96 and were nominally significant ($P \leq 0.0023$; Table 18). The percentage of patients who had at least a 5% or 10% relative improvement in $ppFEV_1$ is shown in Figure 26. For both thresholds, approximately twice as many patients had improvement in $ppFEV_1$ after receiving LUM/IVA compared to placebo.

Figure 26 Percentage of Patients With At Least a 5% or 10% Relative Improvement in $ppFEV_1$, Pooled Studies 103 and 104, FAS



7.7.2 Pulmonary Exacerbations

A pulmonary exacerbation was defined in the study protocol as a new or change in antibiotic therapy for any 4 or more signs or symptoms (e.g., change in sputum, new or increased hemoptysis, increased cough, increased dyspnea; sinus pain or tenderness, radiographic changes indicative of pulmonary infection).[31]

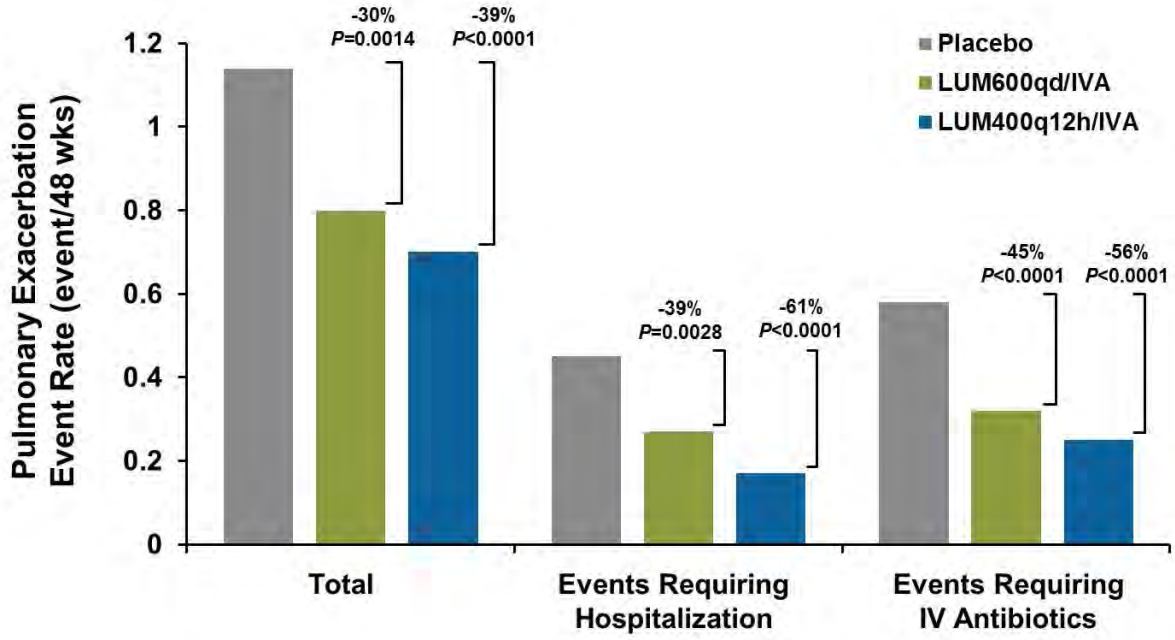
Treatment with LUM/IVA substantially decreased the number of pulmonary exacerbations, including severe pulmonary exacerbations (those requiring hospitalizations or IV antibiotic therapy), and delayed the onset of pulmonary exacerbations.

In Studies 103 and 104, analysis of the key secondary endpoint, number of pulmonary exacerbations, showed that treatment with LUM/IVA resulted in reductions that ranged from 28% to 43% compared to placebo (rate ratios ranged from 0.57 to 0.72; Table 18). These reductions were nominally significant for both LUM/IVA regimens in Study 104 ($P \leq 0.0116$) and for the LUM400q12h/IVA regimen in Study 103 ($P = 0.0169$). In both studies, reductions in pulmonary exacerbations consistently favored the LUM400q12h/IVA regimen.

In the pooled analysis, a greater reduction in pulmonary exacerbations compared to placebo was also observed in the LUM400q12h/IVA regimen (39%; rate ratio: 0.61) than the LUM600qd/IVA regimen (30%; rate ratio: 0.70) (see Figure 27).

Significant and clinically meaningful reductions in severe pulmonary exacerbations (those requiring hospitalization or use of IV antibiotics) were observed with both LUM/IVA regimens with the greatest reductions observed with the LUM400q12h/IVA regimen. Compared to placebo, the rate of pulmonary exacerbations requiring hospitalization was reduced by 39% (LUM600qd/IVA) and 61% (LUM400q12h/IVA), and the rate of pulmonary exacerbations requiring IV antibiotics was reduced by 45% (LUM600qd/IVA) and 56% (LUM400q12h/IVA) (see Figure 27).

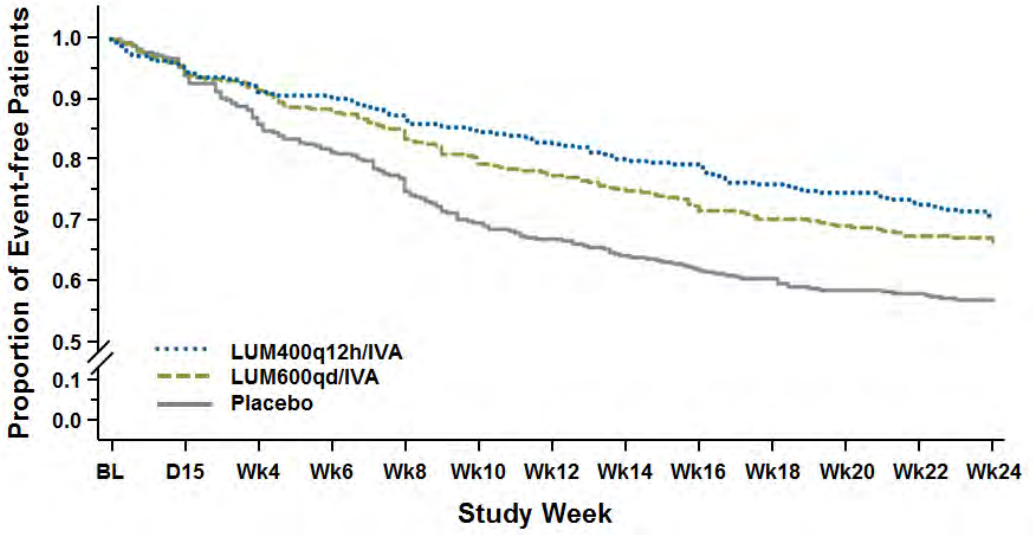
Figure 27 Reduction in Pulmonary Exacerbation Rates by LUM/IVA, Pooled Studies 103 and 104, FAS



Note: Number of patients in each treatment group: placebo = 371, LUM600qd/IVA = 368, LUM400q12h/IVA = 369.

Time-to-first pulmonary exacerbation through Week 24 was a secondary endpoint. As shown in Figure 28, pooled analysis of this endpoint showed that the proportion of patients free of exacerbations across the 24-week treatment period was greater for both LUM/IVA regimens compared to placebo. Hazard ratios compared to placebo favored both LUM/IVA regimens and were statistically significant: the LUM600qd/IVA regimen had a hazard ratio of 0.71 ($P = 0.0040$), and the LUM400q12h/IVA regimen had a hazard ratio of 0.61 ($P<0.0001$).

Figure 28 Time-to-First Pulmonary Exacerbation, Pooled Studies 103 and 104, FAS



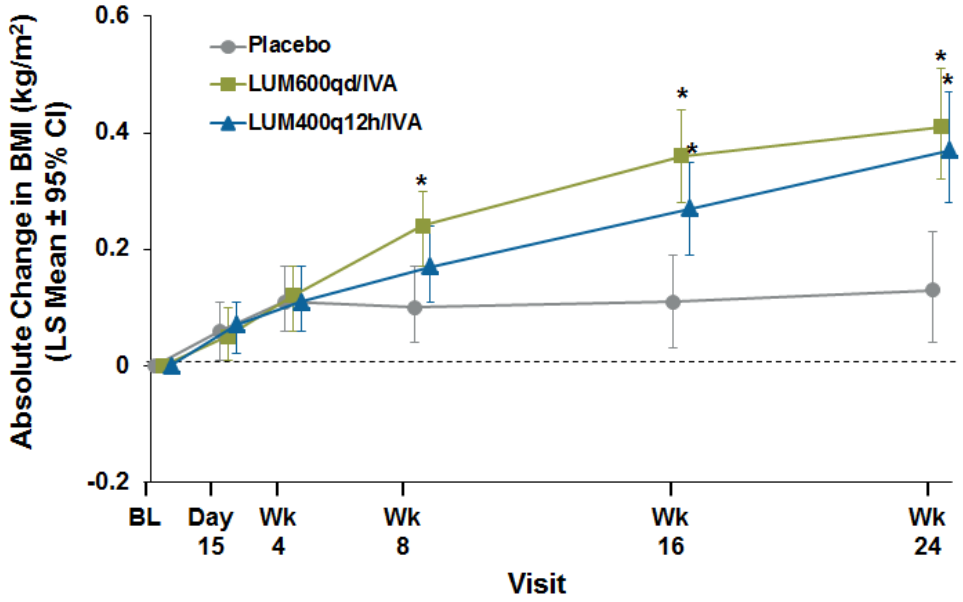
7.7.3 Body Mass Index

An increase in BMI is a measure of improved nutritional status and was an endpoint in previous clinical studies of CFTR-targeted therapies.

Change in BMI was a key secondary endpoint. In Study 104, significant improvements in BMI ranging from 0.36 to 0.41 mg/kg^2 were observed for both LUM/IVA regimens versus placebo ($P\leq0.0001$; Table 18). Although statistical significance was not achieved in Study 103, the treatment effect compared to placebo favored LUM/IVA.

In the pooled analysis, improvements in BMI were observed in all treatment groups, including placebo, over the first 4 weeks of the study, followed by continued improvements with the 2 LUM/IVA regimens (Figure 29). At Week 24, the treatment differences relative to placebo were similar for both LUM/IVA regimens (range: 0.24 to 0.28 kg/m^2) and significant ($P\leq0.0004$; Table 18).

Figure 29 Absolute Change From Baseline in BMI at Each Visit, Pooled Studies 103 and 104, FAS



* indicates $P<0.0250$ compared to placebo

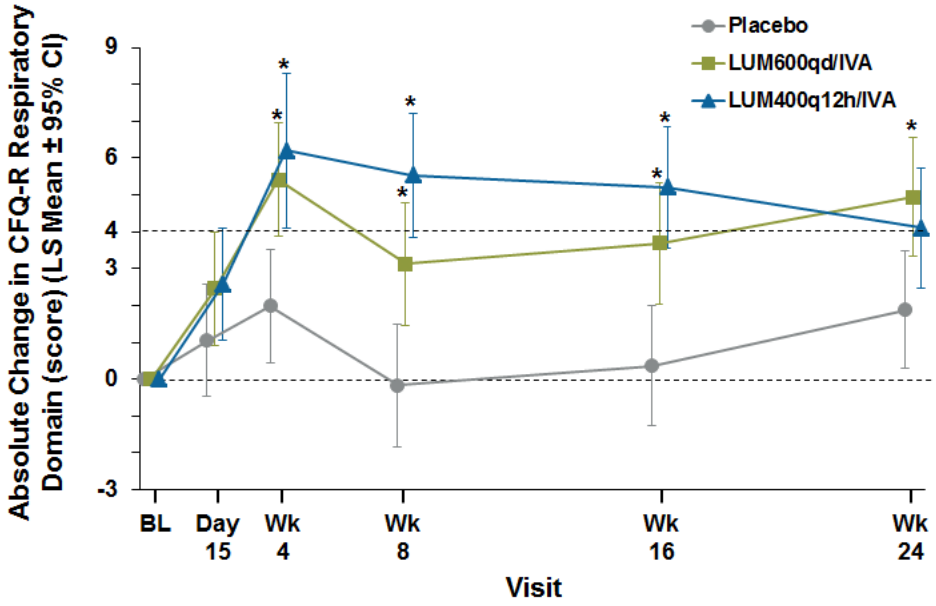
7.7.4 CFQ-R Respiratory Domain

The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF.[68,69,70]

Change in CFQ-R respiratory domain score was a key secondary endpoint. In Studies 103 and 104, improvements in CFQ-R consistently favored LUM/IVA with treatment differences ranging from 1.5 to 3.9 points. Nominal significance was achieved in Study 103 with the LUM600qd/IVA regimen ($P = 0.0168$; Table 18).

As shown in Figure 30, pooled analysis showed improvements in CFQ-R that consistently favored LUM/IVA for both dosing regimens. Within-group improvements were close to or above the MCID of 4. Statistical significance for the treatment difference compared to placebo at Week 24 was only achieved for the LUM600qd/IVA regimen ($P = 0.0071$; Table 18).

Figure 30 Absolute Change in CFQ-R Respiratory Domain Score at Each Visit, Pooled Studies 103 and 104, FAS



* indicates $P<0.0250$ compared to placebo

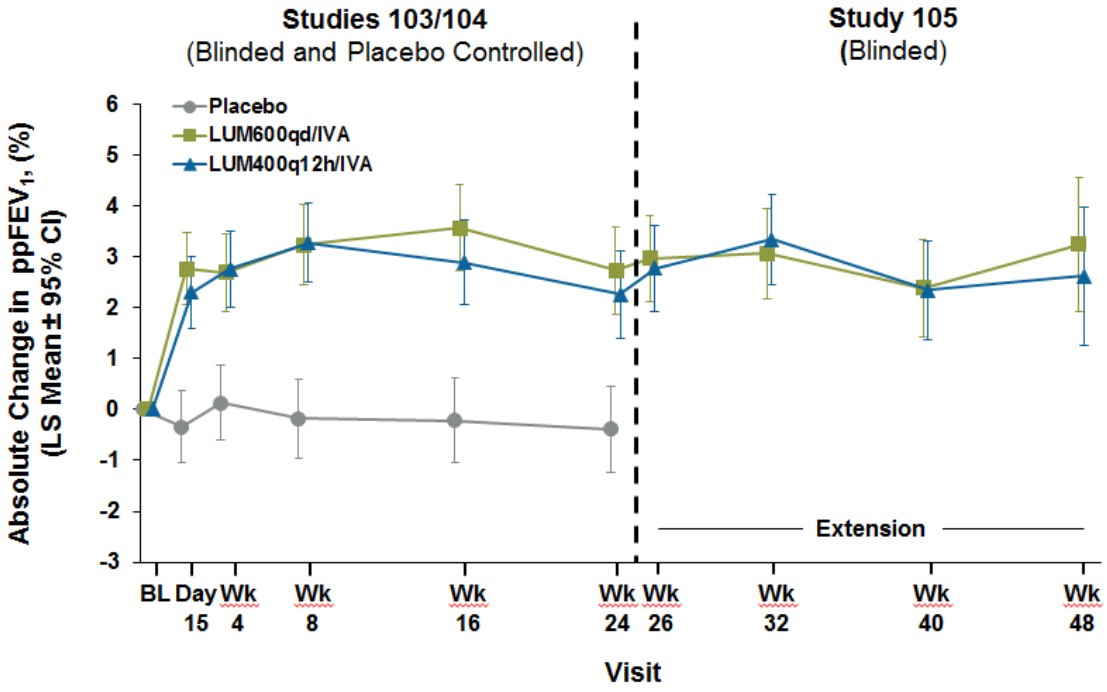
7.8 Durability of Efficacy

The persistence of efficacy was evaluated in Studies 103 and 104 through 24 weeks of treatment and in an ongoing, long-term, Phase 3 rollover study (Study 105).

An interim analysis of Study 105 was performed after approximately 100 patients had been exposed to LUM/IVA for approximately 48 weeks (in Study 103 or 104 plus Study 105). A total of 1027 patients were included in the analysis. At the time of the interim analysis, 5.3% patients had discontinued the study. Of the patients who were randomized to the LUM/IVA groups in Study 103 or 104, 604 patients had completed at least the Week 16 Visit, and 194 patients had completed the Week 24 visit of Study 105.

The rapid and sustained improvements in ppFEV$_1$ observed in patients treated with LUM/IVA combination therapy for 24 weeks in Studies 103 and 104 were durable after an additional 24 weeks of treatment in Study 105 (Figure 31), for a total of 48 weeks of combination treatment.

Figure 31 Durability of ppFEV$_1$ Response, Study 105, FAS



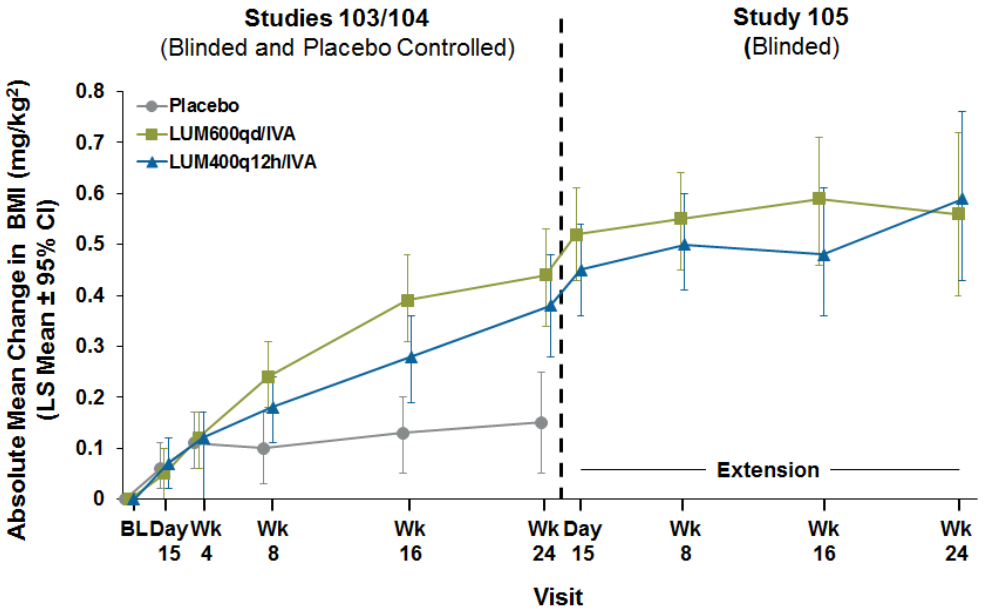
Note: Studies 103, 104, and 105 were blinded studies; patients and study site staff were blinded to individual treatment assignment in Studies 103 and 104 and to the dose group in Study 105.

	Number of Patients (Study 105)			
	Day 15	Wk 8	Wk 16	Wk 24
LUM600qd/IVA	319	308	291	95
LUM400q12h/IVA	317	316	283	88

The interim analysis of Study 105 also provides additional confirmation of the efficacy of LUM/IVA in patients treated for up to 24 weeks with placebo in Study 103 or 104, who then transitioned to active treatment in the rollover study, while still blinded to both the treatment regimen received in Study 103 or 104 and the treatment regimen received in Study 105. In these patients, the magnitude of improvement in ppFEV$_1$ after LUM/IVA combination therapy in Study 105 was similar to the improvement observed in patients who received LUM/IVA in Studies 103 and 104.

Improvements in BMI were also sustained for up to 48 weeks with both LUM/IVA regimens (Figure 32) demonstrating the durability of improved systemic nutritional status with LUM/IVA combination therapy.

Figure 32 Absolute Change From Baseline in BMI, Study 105, FAS



	Number of Patients (Study 105)			
	Day 15	Wk 8	Wk 16	Wk 24
LUM600qd/IVA	328	327	295	97
LUM400q12h/IVA	338	331	281	91

7.9 Exposure-Response for Changes in ppFEV1 in Phase 3

Combination exposure-response models were unable to define the relationship between $ppFEV_1$ and LUM or IVA PK parameters. Therefore, a linear-effect model of absolute change from baseline in $ppFEV_1$ and individual predicted $AUC_{0\text{-}24h}$ values was used to characterize the exposure response for $ppFEV_1$. Overall, the model demonstrated a robust drug effect; however, it did not reveal robust relationships between any specific PK parameter and $ppFEV_1$.

8 SAFETY

Summary

- The safety database included 1839 people from 17 clinical studies of LUM monotherapy and/or LUM/IVA combination therapy, including 738 patients with CF treated with LUM/IVA combination therapy in Studies 103 and 104, and 177 patients with CF treated with LUM/IVA combination therapy in Study 105.
- The safety profile of LUM/IVA is best summarized based on the pooled data from Studies 103 and 104 and data from Study 105.
- The most common risks associated with LUM/IVA treatment have been well characterized in a robust safety database, can be readily monitored and recognized, and may be generally managed without treatment discontinuation.

Studies 103 and 104

- The most common AE was infective pulmonary exacerbation of CF, which occurred at a lower incidence in the LUM/IVA group (37.5%) than in the placebo group (49.2%).
- The incidence of SAEs was lower in the LUM/IVA group (20.1%) than the placebo group (28.6%).
- Overall, the frequency of discontinuations due to AEs was low, but was higher in the LUM/IVA group (4.2%) than in the placebo group (1.6%).
- Respiratory AEs were more frequent in the total LUM/IVA group (26.3%) than the placebo group (17.0%), with the majority of events occurring within the first week of treatment. These events usually resolved within 1 to 2 weeks, and led to treatment discontinuation in only 5 patients in Studies 103 and 104.
- Elevations in transaminases were balanced in patients with CF in both the LUM/IVA and placebo groups across several thresholds.
    - Seven patients in the total LUM/IVA group had SAEs related to elevated liver enzymes or hepatobiliary disorders versus no patients in the placebo group. While all 7 patients had risk factors and alternative etiologies potentially linked to the SAEs, a role for LUM/IVA cannot be excluded.
    - Among 7 patients with hepatic cirrhosis and/or portal hypertension who received LUM/IVA, 1 patient developed hepatic encephalopathy. As a role for LUM/IVA in this event cannot be excluded, the proposed labeling includes recommendations regarding using LUM/IVA with caution in patients with advanced liver disease.

Study 105

- Continued treatment with LUM/IVA combination therapy did not give rise to any safety findings that differed from treatment in Studies 103 and 104.
- One death occurred in a patient who had a life-threatening AE of pulmonary exacerbation; the event was not considered related to study drug.

8.1 Nonclinical Data

LUM and IVA were thoroughly evaluated in a battery of safety pharmacology studies, as well as in acute, repeat-dose, genetic, carcinogenicity, developmental and reproductive studies. In standard in vitro assays for off-target effects suggest that a high degree of selectivity, which when combined with results of safety pharmacology studies suggest a low potential to have biologically detrimental effects on vital function when LUM and IVA are administered in combination. Repeat-dose toxicity studies in mice up to 3 months (subchronic), rats, up to 6 months (chronic) in duration failed to identify any target organs of LUM-related toxicity at dose levels up to and exceeding the subchronic maximum tolerated doses established in these species. Toxicity studies ranging from acute to chronic duration were conducted previously in support of the registration of Kalydeco, which identified adverse effects in the liver of mice and rats at high exposures. These effects are believed to result from rodent-specific accumulation of IVA in the liver. Combination repeat-dose toxicity studies involving the coadministration of LUM and IVA were conducted to assess the potential for additive and/or synergistic toxicity in support of the proposed combination regimen. Based on the available data, the combination regimen was considered safe for chronic administration in humans.

LUM was non-carcinogenic in the short-term alternative 26-week Tg.rasH2 transgenic mouse carcinogenicity assay. IVA was also non-carcinogenic in the 2-year rodent bioassays previously conducted in support of the registration of Kalydeco. Based on the available data and acknowledging that the 2-year rat carcinogenicity study for LUM is ongoing, the overall carcinogenic risk associated with the combination regimen is considered low.

The overall conclusions from reproductive and developmental toxicity studies evaluating LUM indicate that it is not a reproductive and/or developmental toxicant. When evaluated in a similar set of studies to support registration of Kalydeco, IVA was considered to have only minimal effects on female reproduction and fetal development in rats attributable to significant maternal toxicity, and it is associated with ocular toxicities in juvenile animals. Based on the available data, the overall reproductive and developmental risk associated with the combination regimen is considered low for patients age 12 years and older who are *F508del* homozygous.

8.2 Safety Population and Extent of Exposure

The safety profile of LUM/IVA combination therapy has been well characterized within the development program, commensurate with the size of the target population. The safety population consisted of 1839 people from 17 clinical studies (Appendix 12.2). A total of 1615 people received LUM/IVA combination therapy, including 1349 patients with CF. In Studies 103 and 104, 738 patients were randomized to receive LUM/IVA for 24 weeks (369 patients received LUM600qd/IVA and 369 patients received LUM400q12h/IVA). In Study 105, an additional 353 patients who had received placebo in Study 103 or 104 received LUM/IVA in Study 105 (177 patients received LUM600qd/IVA and 176 patients received LUM400q12h/IVA).

The safety profile of LUM/IVA is best summarized based on the pooled data from Studies 103 and 104, which are the largest and longest placebo-controlled studies in the clinical program. Data from Studies 103 and 104 were pooled because of the similarity of the study design, population, and treatment regimens in the 2 studies.

Of the 1054 patients who completed treatment in Study 103 or 104 and thus were eligible to enroll in Study 105, 1050 patients enrolled in Study 105, a long-term safety and efficacy rollover study. A total of 1031 patients enrolled in the treatment cohort, and 19 enrolled in the observational cohort (the observational cohort is not discussed further in this document as these patients did not receive LUM/IVA combination therapy in Study 105). An interim analysis of Study 105 was conducted when approximately 100 patients had been exposed to LUM/IVA for approximately 48 weeks (Study 103 or 104 plus Study 105) to provide additional safety data in support of the NDA. At the time of the data snapshot for the interim analysis (21 July 2014), data for the first 116 patients (treatment cohort) who had completed the Week 24 visit in Study 105 were assessed. Of the 116 patients, 83 patients received 48 weeks of LUM/IVA and 116 patients received 40 weeks of LUM/IVA (58 patients in the LUM400q12h/IVA group and 58 patients in the LUM600qd/IVA group) (subset of patients in the long-term safety dataset).

8.3 Adverse Events in Studies 103 and 104

The sections below are based on treatment-emergent AEs, defined as any AE that increased in severity or that was newly developed at or after initial dosing of study drug to 28 days after the last dose of study drug (hereafter referred to as AEs) in Studies 103 and 104.

8.3.1 Summary of Adverse Events

Table 19 summarizes the incidence of AEs in pooled Studies 103 and 104. There were no deaths. The incidence of serious adverse events (SAEs) was lower in the total LUM/IVA group (20.1%) than the placebo group (28.6%).

Table 19 Summary of AE Incidence: Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
	Placebo	**LUM600qd/IVA**	**LUM400q12h/IVA**	**Total**
	N = 370	**N = 369**	**N = 369**	**N = 738**
Patients With:	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total number of AEs[a]	2132	2167	2130	4297
Any AEs	355 (95.9)	356 (96.5)	351 (95.1)	707 (95.8)
AEs leading to treatment discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)
AEs leading to treatment interruption	25 (6.8)	20 (5.4)	22 (6.0)	42 (5.7)
Grade 3 or 4 AEs	59 (15.9)	57 (15.4)	45 (12.2)	102 (13.8)
SAEs	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
Related SAEs[b]	8 (2.2)	8 (2.2)	14 (3.8)	22 (3.0)
AEs leading to death	0	0	0	0

Note: When summarizing n (%) patients, multiple events were counted only once in that category.

[a] For the calculation of the total number of events, patients with multiple events within a category were counted multiple times in that category.

[b] Related AEs include related, possibly related, and missing categories.

8.3.2 Common Adverse Events

Table 20 shows AEs with an incidence of at least 10% in any treatment group in the pooled Studies 103 and 104. The most common AEs were infective pulmonary exacerbation of CF, cough, headache, and sputum increased. AEs with an incidence at least 3 percentage points higher in the total LUM/IVA group than the placebo group were dyspnea (14.0% versus 7.8%), respiration abnormal (9.8% versus 5.9%), flatulence (6.0% versus 3.0%), and rash (5.6% versus 1.9%). While observed at rates slightly more frequent than placebo, rashes were characteristically mild to moderate, localized reactions and nonserious; with none suggestive of a more severe, exfoliative type of skin reaction. Similar events of rash were also observed in patients treated with IVA monotherapy.

Table 20 AEs With Incidence of At Least 10% in Any Treatment Group, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Preferred Term	Placebo N = 370 n (%)	LUM600qd/IVA N = 369 n (%)	LUM400q12h/IVA N = 369 n (%)	Total N = 738 n (%)
Patients with any AE	**355 (95.9)**	**356 (96.5)**	**351 (95.1)**	**707 (95.8)**
Infective pulmonary exacerbation of CF	182 (49.2)	145 (39.3)	132 (35.8)	277 (37.5)
Cough	148 (40.0)	121 (32.8)	104 (28.2)	225 (30.5)
Headache	58 (15.7)	58 (15.7)	58 (15.7)	116 (15.7)
Sputum increased	70 (18.9)	55 (14.9)	54 (14.6)	109 (14.8)
Dyspnea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Hemoptysis	50 (13.5)	52 (14.1)	50 (13.6)	102 (13.8)
Diarrhea	31 (8.4)	36 (9.8)	45 (12.2)	81 (11.0)
Nausea	28 (7.6)	29 (7.9)	46 (12.5)	75 (10.2)
Respiration abnormal	22 (5.9)	40 (10.8)	32 (8.7)	72 (9.8)
Nasopharyngitis	40 (10.8)	23 (6.2)	48 (13.0)	71 (9.6)
Oropharyngeal pain	30 (8.1)	44 (11.9)	24 (6.5)	68 (9.2)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)	61 (8.3)
Nasal congestion	44 (11.9)	33 (8.9)	24 (6.5)	57 (7.7)

Note: A patient with multiple events within a preferred term category were counted only once in that category. Shaded rows indicate AEs that were higher in the total LUM/IVA group where there was at least 1 percentage point difference from the placebo group.

Table 21 shows the AEs for which the incidence was ≥5% in the total LUM/IVA group and the difference from the placebo group was at least 1 percentage point.

Table 21 AEs with Incidence ≥5% in Total LUM/IVA Group and ≥1 Percentage Point Higher Than in Placebo Group, Pooled Studies 103 and 104, Safety Set

Adverse Reaction (Preferred Term)	Placebo N = 370 n (%)	LUM/IVA N = 738 n (%)
Dyspnea	29 (7.8)	103 (14.0)
Diarrhea	31 (8.4)	81 (11.0)
Nausea	28 (7.6)	75 (10.2)
Respiration abnormal	22 (5.9)	72 (9.8)
Oropharyngeal pain	30 (8.1)	68 (9.2)
Upper respiratory tract infection	20 (5.4)	61 (8.3)
Rhinitis	18 (4.9)	46 (6.2)
Flatulence	11 (3.0)	44 (6.0)
Rash	7 (1.9)	41 (5.6)
Rhinorrhea	15 (4.1)	38 (5.1)
Vomiting	11 (3.0)	37 (5.0)

8.4 Serious Adverse Events and Adverse Events Leading to Discontinuation or Interruption of Study Drug Dosing

8.4.1 Deaths

There were no deaths in Study 103 or 104.

8.4.2 Serious Adverse Events

Table 22 shows the incidence of SAEs that occurred in at least 3 patients in any treatment group in pooled Studies 103 and 104. The most common SAE (at least 10% incidence) in any treatment group was infective pulmonary exacerbation of CF. The incidence of this SAE was lower in the total LUM/IVA group (13.0%) than in the placebo group (24.1%). The only SAEs that occurred in at least 0.5% of patients in the total LUM/IVA group and that had a higher incidence than the placebo group included elevated liver transaminases, hepatobiliary events, and respiratory events (Section 8.6.2).

Table 22 Incidence of SAEs in At Least 3 Patients in Any Treatment Group, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Preferred Term	Placebo N = 370 n (%)	LUM600qd/IVA N = 369 n (%)	LUM400q12h/IVA N = 369 n (%)	Total N = 738 n (%)
Patients with Any SAEs	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
Infective pulmonary exacerbation of CF	89 (24.1)	55 (14.9)	41 (11.1)	96 (13.0)
Hemoptysis	3 (0.8)	4 (1.1)	5 (1.4)	9 (1.2)
Elevated liver transaminases[a]	0	4 (1.1)	3 (0.8)	7 (0.9)
Respiratory events[b]	0	4 (1.1)	0	4 (0.5)
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)	2 (0.5)	4 (0.5)

Note: A patient with multiple events within a category was counted only once in that category. Table is sorted in descending order of the Total LUM/IVA column by preferred term.

[a] Term includes cholestasis/hepatitis, elevated ALT/AST, elevated liver enzymes, hepatic encephalopathy, hepatitis cholestatic, and liver function test abnormal

[b] Term includes bronchospasm and dyspnea

8.4.3 Adverse Events Leading to Discontinuation of Study Drug

The incidence of AEs that led to discontinuation of study drug in pooled Studies 103 and 104 is provided in Table 23. The incidence of AEs leading to study drug discontinuation was higher in the total LUM/IVA group (4.2%) than in the placebo group (1.6%). The most common AEs that led to discontinuation were respiratory events (Section 8.6.1), blood CPK increased (Section 8.5), elevated liver transaminases (Section 8.6.1), and hemoptysis.

Table 23 AEs Leading to Discontinuation of Study Drug in 3 or More Patients, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Preferred Term	Placebo N = 370 n (%)	LUM600qd/IVA N = 369 n (%)	LUM400q12h/IVA N = 369 n (%)	Total N = 738 n (%)
Patients with Any AEs Leading to Treatment Discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)
Respiratory events[a]	0	5 (1.4)	0	5 (0.7)
Blood creatine phosphokinase increased	0	0	4 (1.1)	4 (0.5)
Elevated liver transaminases[b]	0	3 (0.8)[c]	1 (0.3)	4 (0.5)
Hemoptysis	2 (0.5)	0	3 (0.8)	3 (0.4)

[a] Term includes respiration abnormal, bronchospasm, and dyspnea

[b] Term includes cholestasis/hepatitis, elevated ALT/AST, elevated liver enzymes, hepatic encephalopathy, hepatitis cholestatic, and liver function test abnormal. Elevated ALT/AST, elevated liver enzymes; however, did not lead to discontinuation of study drug.

[c] One subject had an SAE of cholestasis and hepatitis at the Week 24 visit. Study drug was withdrawn for this subject but was not captured as a treatment discontinuation in the clinical database because the subject had completed the protocol-defined treatment.

8.5 Laboratory Evaluations, Vital Signs, and Other Safety Evaluations

Patients with CF are chronically ill, experience frequent infections, take numerous medications, and have disease-related metabolic abnormalities. Thus, fluctuations in laboratory parameters are common.[71] The incidence of laboratory abnormalities resulting in reports of AEs was generally similar between the LUM/IVA and placebo groups (Table 24). The descriptive statistics and incidence of potentially significant laboratory values for the majority of the clinical laboratory parameters (serum chemistry, hematology, and coagulation studies), vital signs, physical examinations, and ECGs assessed in pooled Studies 103 and 104 showed minor differences between the LUM/IVA and placebo groups that were not considered to be clinically meaningful.

Table 24 Incidence of Subset of Chemistry Laboratory AEs, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
	Placebo	**LUM600qd/IVA**	**LUM400q12h/IVA**	**Total**
	N = 370	**N = 369**	**N = 369**	**N = 738**
Subjects with:	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any laboratory AE in system organ class "Investigations"	**94 (25.4)**	**76 (20.6)**	**84 (22.8)**	**160 (21.7)**
Blood CPK increased	20 (5.4)	14 (3.8)	27 (7.3)	41 (5.6)
Elevated transaminases AESI	17 (4.6)	18 (4.9)	20 (5.4)	38 (5.1)
Blood creatinine increased	5 (1.4)	4 (1.1)	2 (0.5)	6 (0.8)
Blood glucose increased	2 (0.5)	4 (1.1)	1 (0.3)	5 (0.7)
Blood glucose decreased	3 (0.8)	1 (0.3)	3 (0.8)	4 (0.5)
Vitamin D decreased	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)
Blood IgE increased	2 (0.5)	1 (0.3)	0	1 (0.1)
Blood ALP increased	5 (1.4)	0	1 (0.3)	1 (0.1)
Blood LDH increased	2 (0.5)	1 (0.3)	0	1 (0.1)

Note: Elevated transaminases AESIs (adverse events of special interest) included events of ALT abnormal, ALT increased, AST abnormal, AST aminotransferase increased, transaminases abnormal, transaminases increased, LFT abnormal, hypertransaminasemia, hepatic function abnormal, hepatic enzyme increased, and hepatic enzyme abnormal.

Creatine Phosphokinase

Table 25 provides the incidence of creatine phosphokinase (CPK) elevations and AEs in Studies 103 and 104. The incidence of the adverse event of blood CPK increased was similar in the total LUM/IVA (5.6%) and placebo (5.4%) groups. Nonetheless, only events which were considered SAEs (2 patients) or led to discontinuation (4 patients) were observed with LUM/IVA (overall, 5 patients). The maximum CPK values in patients who discontinued or had an SAE related to CPK ranged from 1271 to 3649 U/L compared with 172 to 34000 U/L in patients who had non-serious AEs in the placebo group and 110 to 31560 U/L in patients who had non-serious AEs in the total LUM/IVA group. The incidence of potential relevant adverse events (e.g., myalgia, fatigue) was similar in patients who had SAEs or AEs leading to discontinuations and patients with non-serious AEs in the placebo and total LUM/IVA

groups. Overall the data regarding CPK elevations do not suggest an association with LUM/IVA combination therapy.

Table 25 Incidence of Creatine Phosphokinase Elevations and AEs, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
	Placebo	LUM600qd/IVA	LUM400q12h/IVA	Total
	N = 370	N = 369	N = 369	N = 738
Patients with:	n (%)	n (%)	n (%)	n (%)
CPK >3×ULN to ≤10×ULN	18 (4.9)	11 (3.0)	18 (4.9)	29 (4.0)
CPK >10×ULN	10 (2.7)	7 (1.9)	10 (2.7)	17 (2.3)
AE: CPK increased	20 (5.4)	14 (3.8)	27 (7.3)	41 (5.6)
SAE: CPK increased	0	0	2 (0.5)	2 (0.3)
AE that led to discontinuation of study drug : CPK increased	0	0	4 (1.1)	4 (0.5)

8.6 Adverse Events of Special Interest

AEs of special interest (AESIs) were created for respiratory symptoms and transaminase elevations.

8.6.1 Respiratory Symptoms

The respiratory symptom AESI was created to explore select AEs within the respiratory system (chest discomfort, dyspnea, respiration abnormal [verbatim term: respiratory chest tightness], asthma, bronchial hyper-reactivity, bronchospasm, and wheezing).

Table 26 shows the incidence of respiratory symptom AESIs. The majority of these events were mild to moderate in severity and resolved without treatment discontinuation. No subgroups were identified to be at a disproportionate risk for respiratory AESIs.

In pooled Studies 103 and 104, the incidence of respiratory AESIs was higher in the total LUM/IVA group (26.3%) than in the placebo group (17.0%) and was similar in the LUM600qd/IVA group (26.8%) and LUM400q12h/IVA group (25.7%). Four patients in the LUM600qd/IVA group had respiratory AESIs that were SAEs, and 5 patients in the LUM600qd/IVA group discontinued treatment because of a nonserious respiratory AESI (2 patients for dyspnea, 2 patients for bronchospasm, and 1 patient for respiration abnormal).

Table 26 Incidence of Respiratory Symptom AESIs of Special Interest, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Preferred Term	Placebo N = 370 n (%)	LUM600qd/IVA N = 369 n (%)	LUM400q12h/IVA N = 369 n (%)	Total N = 738 n (%)
Any Respiratory AESI	**63 (17.0)**	**99 (26.8)**	**95 (25.7)**	**194 (26.3)**
Dyspnea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Respiration abnormal	22 (5.9)	40 (10.8)	32 (8.7)	72 (9.8)
Wheezing	15 (4.1)	12 (3.3)	11 (3.0)	23 (3.1)
Chest discomfort	5 (1.4)	7 (1.9)	7 (1.9)	14 (1.9)
Asthma	5 (1.4)	4 (1.1)	8 (2.2)	12 (1.6)
Bronchospasm	1 (0.3)	7 (1.9)	5 (1.4)	12 (1.6)
Bronchial hyper-reactivity	0	1 (0.3)	2 (0.5)	3 (0.4)
SAEs of Respiratory AESI	**0**	**4 (1.1)**	**0**	**4 (0.5)**
Respiratory AESI leading to discontinuation of study drug	**0**	**5 (1.4)**	**0**	**5 (0.7)**

Respiratory symptom AEs had an onset predominantly in the first week of treatment, with a median time-to-onset of 2 days in the total LUM/IVA group compared with 43 days in the placebo group. There was no imbalance between the placebo and LUM/IVA groups after Week 1 (Table 27). The median duration of respiratory symptom AESI in the total LUM/IVA group was 6 days, and the median duration of reactive airway AESI in the total LUM/IVA group was 8 days.

Table 27 Timing of Onset of Respiratory Symptom AESIs, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Preferred Term	Placebo N = 370 n (%)	LUM600qd/IVA N = 369 n (%)	LUM400q12h/IVA N = 369 n (%)	Total N = 738 n (%)
Any Respiratory Symptom AE (chest discomfort, dyspnea, or respiration abnormal)	**51 (13.8)**	**88 (23.8)**	**81 (22.0)**	**169 (22.9)**
>0 to ≤1 Week	14 (3.8)	66 (17.9)	65 (17.6)	131 (17.8)
>1 to ≤2 Weeks	4 (1.1)	6 (1.6)	4 (1.1)	10 (1.4)
>2 to ≤8 Weeks	17 (4.6)	6 (1.6)	10 (2.7)	16 (2.2)
>8 to ≤16 Weeks	14 (3.8)	11 (3.0)	8 (2.2)	19 (2.6)
>16 to ≤24 Weeks	9 (2.4)	12 (3.3)	8 (2.2)	20 (2.7)

Data from spirometry assessments performed after dosing with LUM/IVA in healthy subjects (Study 009, Cohort 4) and in patients 6 through 11 years of age with CF who were homozygous for *F508del* mutation (Study 011, Part A) are informative in evaluating these respiratory AESIs. Declines in $ppFEV_1$ (generally not associated with respiratory AEs) were observed within 4 hours of dosing in both studies. In Study 011, lung function returned to near baseline within 7 days of continued dosing. Furthermore, data from Study 009 suggested

that the observed decline in ppFEV$_1$ was ameliorated by treatment with long-acting bronchodilators and reversed by treatment with short-acting inhaled bronchodilators. These observations suggest that the respiratory AESIs may be related to bronchoconstriction, and thus could be managed through the use of bronchodilators. The events of dyspnea and respiration abnormal likely do not pose a significant safety risk given the low incidence of treatment discontinuation related to these AESIs in Studies 103 and 104, and the frequent use of bronchodilators in the target population (92.4% before the first dose of study drug).

8.6.2 Transaminase Elevations and Hepatobiliary Events

Transaminase elevations as well as liver disease are common in CF patients. CF liver disease has been reported to occur in up to 35% of patients with CF, though reports on the prevalence vary widely,[34-36] likely due to the different definitions used, ages studied, and whether the analysis is cross-sectional versus longitudinal. Depending on the study population, cirrhosis is reported in 1.3% to 16.6% of the patients with CF, with the majority of the estimates in the range of 2% to 8%.[72-76] In the US CF patient registry, the prevalence of cirrhosis in 2012 was 2.3%.[77] The reported prevalence of cirrhosis with portal hypertension varies from 1.9% to 4.2%.[76,77] Therefore, background abnormalities in liver function tests (LFTs) were expected in this population and were defined as an AESI.

8.6.2.1 Transaminase Elevations

The overall incidence and patterns of transaminase elevations observed in the Phase 3 studies is typical for patients with CF, and showed no imbalance in transaminase elevations between patients treated with active drug and those on placebo.

The incidence of elevated liver enzymes (>3 × ULN) was low and similar in the total LUM/IVA group (5.2%) and the placebo group (5.1%). Transaminase elevations of >5 × ULN were <2% and >8 × ULN were <1% in both the total LUM/IVA and placebo groups. Compared with no subjects in the placebo group, ALT or AST elevations associated with increases in total bilirubin concentrations occurred in 2 subjects in the LUM600qd/IVA group and 1 subject in the LUM400q12h/IVA group. All 3 cases are complicated by numerous factors, including concurrent medical issues and underlying liver disease, suggesting alternative etiologies (e.g., hepatitis E seroconversion, CF exacerbation, pre-existing cirrhosis and portal hypertension, prior history of transaminase elevations), although a contributory role of LUM/IVA cannot be excluded.

The incidence and pattern of LFT changes in Study 105, with exposure to LUM/IVA combination therapy beyond 24 weeks, did not suggest any new safety findings compared with Studies 103 and 104.

Table 28 Summary of Transaminase Elevations and Bilirubin Elevations, Pooled Studies 103 and 104, Safety Set

Preferred Term	Placebo N = 369 n (%)	LUM/IVA LUM600qd/IVA N = 366 n (%)	LUM/IVA LUm400q12h/IVA N = 368 n (%)	LUM/IVA Total N = 734 n (%)
ALT or AST Increased				
>3 × ULN	19 (5.1)	22 (6.0)	16 (4.3)	38 (5.2)
>3 × to ≤5 × ULN	12 (3.3)	12 (3.3)	11 (3.0)	23 (3.1)
>5 × to ≤8 × ULN	5 (1.4)	7 (1.9)	2 (0.5)	9 (1.2)
>8 × ULN	2 (0.5)	3 (0.8)	3 (0.8)	6 (0.8)
Total Bilirubin Increased				
>1.5 × to ≤2 × ULN	5 (1.4)	0	0	0
>2 × ULN	1 (0.3)	2 (0.5)	0	2 (0.3)
ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN	0	2 (0.5)	1 (0.3)[a]	3 (0.4)

[a] One subject had AST >3 × ULN and total bilirubin >2 × ULN; however, the laboratory data for this subject was not included in the clinical database.

8.6.2.2 Adverse Events

In the pooled placebo-controlled studies, elevated transaminases or hepatobiliary disorder-related AEs occurred in 5.4% of patients in the placebo group and 5.7% of patients in the total LUM/IVA group (Table 29). The incidence of AESIs of elevated transaminases continued to be low in Study 105.

Although individual AEs in the transaminase AESI category did not occur in more than 1 patient, 7 (0.9%) patients in the total LUM/IVA group had SAEs related to elevated liver enzymes or hepatobiliary disorders compared to no patients in the placebo group (Table 29). Four of these SAEs were reported as transaminase elevations, 2 as cholestatic hepatitis, and 1 as hepatic encephalopathy. These cases had a range of complex clinical presentations and were all confounded by alternative etiologies and/or risk factors (e.g., hepatitis E seroconversion, CF exacerbation, pre-existing cirrhosis and portal hypertension, prior history of transaminase elevations). All 7 SAEs resolved, and liver function tests returned to baseline for all subjects following resolution. Study drug dosing was discontinued for 4 patients and interrupted for 3 patients. Of the 3 patients for whom study drug was interrupted, study drug dosing was successfully reinitiated for 2 patients. Although the data do not support a causal association between LUM/IVA and these liver events, a contribution cannot be excluded entirely and recommendations for monitoring and management are included in proposed labeling.

In addition to the transaminase AESIs, review of the data from Studies 103 and 104 revealed enrollment of 8 patients who had a history of hepatic cirrhosis and/or portal hypertension. None of these patients had moderate or severe hepatic impairment by Child-Pugh criteria. (No patients with moderate or severe hepatic impairment by Child-Pugh criteria were included in Phase 3 studies.) Of these 8 patients, 7 were in the total LUM/IVA group (6 patients in the LUM400q12h/IVA group and 1 patient in the LUM600qd/IVA group) and 1 was in the placebo group. Among these patients, worsening liver function with increased

ALT, AST, bilirubin, and hepatic encephalopathy was observed in 1 patient in the LUM400q12h/IVA group. The event occurred within 6 days of the start of dosing and resolved following discontinuation of LUM/IVA. As a role for LUM/IVA in this event cannot be excluded, the proposed labeling includes recommendations regarding use with caution in patients with advanced liver disease only if the benefits are considered to outweigh the risks.

Table 29 Incidence of Liver-Related AEs of Special Interest, Pooled Studies 103 and 104, Safety Set

		LUM/IVA		
Patients with:	**Placebo N = 370 n (%)**	**LUM600qd/IVA N = 369 n (%)**	**LUM400q12h/IVA N = 369 n (%)**	**Total N = 738 n (%)**
Any liver-related AEs	**20 (5.4)**	**20 (5.4)**	**22 (6.0)**	**42 (5.7)**
Any AESI of elevated transaminases	**17 (4.6)**	**18 (4.9)**	**20 (5.4)**	**38 (5.1)**
Alanine aminotransferase increased	9 (2.4)	6 (1.6)	8 (2.2)	14 (1.9)
Aspartate aminotransferase increased	8 (2.2)	6 (1.6)	9 (2.4)	15 (2.0)
Hepatic enzyme increased	0	6 (1.6)	4 (1.1)	10 (1.4)
Liver function test abnormal	6 (1.6)	4 (1.1)	3 (0.8)	7 (0.9)
Transaminases increased	1 (0.3)	1 (0.3)	2 (0.5)	3 (0.4)
AEs related to the liver leading to treatment discontinuation	**0**	**3 (0.8)[a]**	**1 (0.3)**	**4 (0.5)**
SAEs related to the liver	**0**	**4 (1.1)**	**3 (0.8)**	**7 (0.9)**

Note: Patients with multiple events in a category were counted only once in that category.

[a] One patient had SAEs of cholestasis and hepatitis at the Week 24 visit. Study drug was withdrawn but was not captured as a treatment discontinuation because the patient had completed protocol-defined treatment.

8.6.2.3 Exposure Response

Exposure-dependent changes in ALT and AST were evaluated using several exposure response models; however, no relationship was identified. Therefore, a simple offset model was implemented to describe changes in ALT and AST in response to LUM/IVA treatment as drug effect (drug effect term, no exposure parameter) and placebo. Model predicted changes in ALT and AST for both LUM/IVA groups were similar to, or less than, those observed in the placebo group.

8.7 Long-Term Safety Data

The continued treatment with LUM/IVA in Study 105 did not give rise to any safety findings that differed from the 24 weeks of treatment in Studies 103 and 104.

One death occurred: a 24-year old female who received LUM400q12h/IVA in the previous study. The patient had a life-threatening AE of pulmonary exacerbation on Day 344 of dosing. Study drug was withdrawn due the AE. On Day 366, the patient died due to respiratory failure. The investigator considered the event not related to study drug.

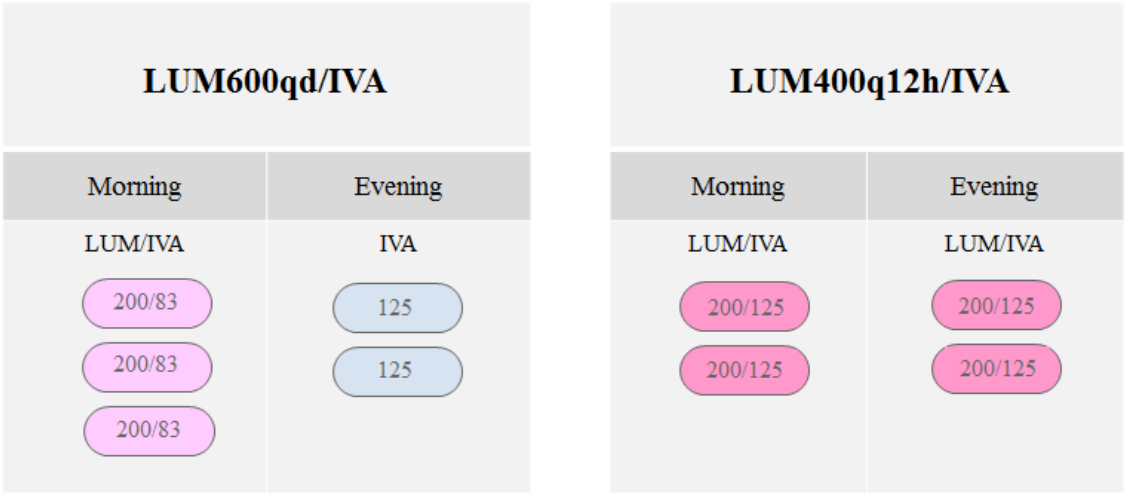
9 RECOMMENDED DOSAGE

The efficacy results in Studies 103 and 104 were consistent across the 2 dose regimens and studies, with the only consistent differentiation between the 2 active regimens being the consistently greater reduction in pulmonary exacerbations, including those requiring hospitalization or the use of IV antibiotics, seen with the LUM400q12h/IVA regimen.

The LUM400q12h/IVA regimen has a 33% higher total daily dose of LUM than the LUM600qd/IVA regimen; thus, the difference in exposure is modest, with a lower peak-to-trough ratio and approximately 2-fold higher LUM trough concentration due to the q12h regimen. Both LUM regimens are given with an IVA dosage of 250 mg q12h. PK/PD analyses of pooled Phase 3 study data do not reveal any robust relationships between any specific PK parameter and key efficacy or safety outcomes. PK/PD analyses of sweat chloride response in Phase 2 suggests that the higher LUM concentrations for the LUM400q12h/IVA regimen will result in a greater reduction of sweat chloride than with the LUM600qd/IVA, suggesting a greater amount of CFTR modulation with this regimen. There are no meaningful differences in the overall safety profile of the LUM/IVA combination therapy dose regimens studied in Phase 3.

The LUM400q12h/IVA regimen has an important advantage for use in the "real world" setting outside a controlled clinical study, due to the fully-FDC regimen of 2 tablets to be taken every 12 hours (Figure 33). A posology consisting of 2 identical FDC tablets given both in the morning and the evening has the potential to reduce dosing errors and improve patient adherence with the regimen in general day-to-day practice.

Figure 33 Phase 3 Dosing Regimens



Thus, the LUM400q12h/IVA regimen is proposed to have the better overall benefit:risk profile for authorization and commercialization. The recommended dosage is therefore LUM400q12h/IVA (800 mg total daily dose of LUM and 500 mg total daily dose of IVA) taken with fat-containing food for patients with CF age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

10 BENEFIT AND RISK CONCLUSIONS

- LUM/IVA combination therapy had beneficial effects on pulmonary function, pulmonary exacerbations, patient-reported outcomes, and nutritional measures (BMI and weight) in patients 12 years of age and older with CF who are homozygous for the *F508del* mutation.
- Importantly, these effects were observed while patients continued on their usual prescribed therapies for CF.
- The treatment effects favored LUM/IVA across all subgroups, including patients who have a $ppFEV_1$ below 40 at baseline, and for all primary and key secondary endpoints in the 2 large, pivotal Phase 3 studies.
- The effect of LUM/IVA persisted up to approximately 48 weeks and was reproducible in patients who were previously receiving placebo.
- The safety profile of LUM/IVA was characterized by AEs that were most often mild to moderate in severity. The most common risks of LUM/IVA identified in the clinical and nonclinical studies are readily monitored and recognized, and may be managed without treatment discontinuation.
- Respiratory adverse events were more frequent in the total LUM/IVA group than the placebo group, with the majority of events occurring within the first week of treatment. Although the etiology is unknown, these respiratory events are likely associated with LUM/IVA treatment. These events usually resolved within 1 to 2 weeks, and led to treatment discontinuation in only 5 patients in the pooled placebo-controlled Phase 3 studies.
- Elevations in transaminases were observed in CF patients in both the LUM/IVA and placebo groups, consistent with the natural history of CF liver disease. Because the role of LUM/IVA in these events is uncertain, monitoring and management recommendations will be included in the product labeling. There was no apparent relationship between higher exposure to LUM/IVA and the occurrence of transaminase elevations in patients exposed to LUM/IVA compared with exposure in patients without transaminase elevations.
- More patients in the total LUM/IVA group had SAEs related to elevated liver enzymes or hepatobiliary disorders, including 3 patients with transaminase elevations associated with increases in total bilirubin; all 3 patients had confounded clinical histories. Underlying risk factors and alternative etiologies complicate assessment of the SAEs, and the role of LUM/IVA in causing or contributing to transaminase elevations and hepatobiliary SAEs cannot be excluded.
- LUM is a strong inducer of CYP3A and IVA is a sensitive CYP3A substrate. Guidance for the management of observed and anticipated DDIs is provided in the proposed labeling.

- Improvements in pulmonary exacerbation-related outcomes, including those requiring hospitalization or IV antibiotic use, consistently favored the LUM400q12h/IVA regimen, while there was no clear differentiation between the 2 combination therapy regimens in other efficacy measures. There were no meaningful differences in the overall safety profiles of the regimens evaluated in Phase 3. The LUM400q12h/IVA regimen has an important posology advantage due to the fully-FDC regimen of 2 tablets to be taken twice daily (every 12 hours), which has the potential to reduce dosing errors and improve patient adherence with the regimen in general day-to-day practice.
- The LUM400q12h/IVA regimen has the better overall benefit:risk profile for authorization and commercialization.

The positive benefit/risk profile supports approval of LUM/IVA combination therapy for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation on the *CFTR* gene.

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12 APPENDICES

12.1 Abbreviations and Definitions of Terms

12.1.1 List of Abbreviations

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0\text{-}12h}$	AUC from the time of dosing to 12 hours postdose
$AUC_{0\text{-}24h}$	AUC from the time of dosing to 24 hours postdose
AUC_{τ}	AUC during a dosing interval
BL	baseline
BMI	body mass index
$C_{0h,ave}$	average observed concentration collected predose across study visits
$C_{3\text{-}6h,ave}$	average observed concentration collected 3 to 6 hours postdose across applicable study visits
CDC	Centers for Disease Control
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CI	confidence interval
C_{max}	maximum observed concentration
CPK	creatine phosphokinase
CTN	Clinical Trials Network
CV	coefficient of variation
CYP3A4	cytochrome P4540 3A4
DDI	drug-drug interaction
EC_{50}	concentration at which effect is at half the maximum
ECFS	European Cystic Fibrosis Society
ECG	electrocardiogram
E_{max}	maximum effect
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
FEV_1	forced expiratory volume in 1 second

Abbreviation	Term
GI	gastrointestinal
G551D	missense mutation that results in the replacement of a glycine codon at position 551 of with an aspartic acid residue
G551D	CFTR protein with the replacement of a glycine residue normally found at position 551 of the wild-type protein with an aspartic acid residue
HBE	human bronchial epithelial
ICH	International Conference on Harmonization
IV	intravenous
IVA	ivacaftor
LFT	liver function test
LS	least squares
LUM	lumacaftor
LUM600qd/IVA	lumacaftor 600 mg qd in combination with ivacaftor 250 mg q12h
LUM400q12h/IVA	lumacaftor 400 mg q12h in combination with ivacaftor 250 mg q12h
LUM/IVA	lumacaftor/ivacaftor
M1-IVA	M1 metabolite of ivacaftor
M6-IVA	M6 metabolite of ivacaftor
M28-LUM	M28 metabolite of lumacaftor
MCID	minimal clinically important difference
MMRM	mixed-effects model for repeated measures
NDA	New Drug Application
OATP	organic anion-transporting polypeptide
P-gp	P-glycoprotein
PD	pharmacodynamic, pharmacodynamics
PE	pulmonary exacerbation
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PXR	pregnane-X-receptor
q12h	every 12 hours
qd	daily
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SE	standard error
SEM	standard error of the mean
$t_{½}$	terminal phase half-life
TDN	Therapeutics Development Network
t_{max}	time of the maximum concentration
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
Vertex	Vertex Pharmaceuticals Incorporated

12.1.2 Abbreviated Study Numbers

In the body of the text, study numbers for LUM monotherapy or LUM/IVA combination therapy are abbreviated to the last 3 digits (e.g., Study VX08-809-101 is Study 101). Study numbers for IVA monotherapy are abbreviated to the last 6 digits (e.g., VX08-770-104 is Study 770-104).

12.1.3 Abbreviated Treatment Groups

During the clinical development of LUM, Phase 1 and Phase 2 studies were conducted with lumacaftor monotherapy (LUM) and with lumacaftor in combination with ivacaftor (LUM/IVA). These abbreviations are used without regard to the dosage of formulation (fixed dose combination [FDC] tablets, or separate LUM and IVA tablets) of study drug.

The treatment regimens used in Phase 3 studies were LUM 600 mg qd/IVA 250 mg q12h and LUM 400 mg q12h/IVA 250 mg q12h. These regimens are abbreviated as LUM600qd/IVA and LUM400q12h/IVA.

12.2 Tabular Summary of Clinical Studies Evaluating LUM Monotherapy and/or LUM/IVA Combination Therapy

Study	Study Design	Total Number of Subjects or Patients
Phase 1 Study in Healthy Subjects (Subjects Without CF): LUM Monotherapy		
Study 001	Randomized, double-blinded, single-dose escalation followed by a multiple-dose escalation	64
Study 003	Randomized, open-label, single-dose bioavailability and food effect study of a capsule formulation of VX-809 relative to a suspension formulation of VX-809	18
Study 004	Nonrandomized, open-label, single-dose ADME	6
Phase 1 Study in Healthy Subjects (Subjects Without CF): LUM Monotherapy and LUM/IVA Combination Therapy		
Study 005	Randomized, double-blind, placebo-controlled, multiple-dose, DDI study of VX-809 and VX-770	24
Study 006	Randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation, DDI study of VX-809 and VX-770	48
Study 007	Randomized, open-label, single-dose, crossover, relative bioavailability of a high drug load lumacaftor formulation compared to a lumacaftor reference formulation	61
Study 008	Randomized, double-blind thorough QT	78
Phase 1 Study in Healthy Subjects (Subjects Without CF): LUM/IVA Combination Therapy		
Study 009 Cohorts 1-3	Nonrandomized, open-label, multiple-dose DDI study of ciprofloxacin, itraconazole, and rifampin with lumacaftor in combination with ivacaftor	54
Study 009 Cohort 4	Effect of bronchodilator in combination with LUM/IVA	26
Study 010 Group B	Nonrandomized, open-label, multiple-dose study in subjects with moderate hepatic impairment study	11
Study 010 Group A	Moderate hepatic impairment PK and safety	12
Study 012	Randomized, open-label, single-dose, food effect study	28
Phase 1 Study in Subjects With CF: LUM Monotherapy		
Study 002	Randomized, open-label, single-dose PK study	8
Phase 1 Study in Subjects With CF: LUM/IVA Combination Therapy		
Study 011 Part A	Open-label, PK study in subjects aged 6 through 11 years	10
Phase 2 Studies in Subjects With CF: LUM Monotherapy		
Study 101	Randomized, double-blind, placebo-controlled safety and PK	72
Phase 2 Studies in Subjects With CF: LUM Monotherapy and LUM/IVA Combination Therapy		
Study 102	Randomized, double-blind, placebo-controlled, safety and efficacy	197
Phase 3 Study in Subjects With CF Aged 12 Years and Older: LUM/IVA Combination Therapy		
Study 103	Randomized, double-blind, placebo-controlled, safety and efficacy	549
Study 104	Randomized, double-blind, placebo-controlled, safety and efficacy	559
Study 105	Randomized, double-blind, rollover, long-term safety and efficacy study	1142